Fluoroquinolones: Synthesis and Application

Valery N. Charushin, Emiliya V. Nosova, Galina N. Lipunova, and Oleg N. Chupakhin

Contents

1 Introduction 112
2 Synthesis and Antibacterial Activity of Fluoroquinolones 114
2.1 Bicyclic Fluoroquinolones 114
2.1.1 Modification of the Position N(1) 115
2.1.2 Modification of the Position C(2) 120
2.1.3 Modification of the 3-Carboxyl Group 120
2.1.4 Modification of the 4-Oxo Group 121
2.1.5 Modification of the Position C(5) 122
2.1.6 Modification of the Position C(6) 123
2.1.7 Modification of the Position C(7) 124
2.1.8 Modification of Position C(8) 131
2.2 Polycyclic Fluoroquinolones 132
2.2.1 [*a*]-Annelated Fluoroquinolones 132
2.2.2 [*b*]-Annelated Fluoroquinolones 136
2.2.3 [*c*]- and [*d,e*]-Annelated Fluoroquinolones 137
2.2.4 [*f*]- and [*g*]-Annelated Fluoroquinolones 137
2.2.5 [*h*]-Annelated Fluoroquinolones 137
2.2.6 [*i,j*]-Annelated Fluoroquinolones 138
2.2.7 Tetracyclic [*a,i,j*]-Annelated Fluoroquinolones 141
3 Other Types of Biological Activity of Fluoroquinolones 142
3.1 Anticancer Activity 142
3.2 Tuberculostatic Activity 147
3.3 Antiviral Activity 150
3.4 Other Types of Biological Activity 152
4 Structure and Spectral Characteristics 155
5 Complexes of Fluoroquinolones with Metals 155
References 161

V.N. Charushin • G.N. Lipunova
Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, Ekaterinburg, Russia
e-mail: charushin@ios.uran.ru; lipunova@ios.uran.ru

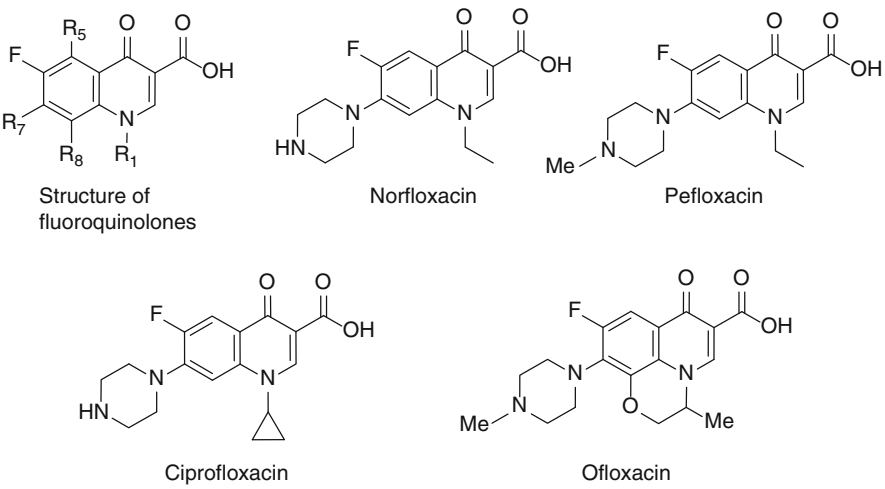
V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*,
DOI 10.1007/978-3-319-04435-4_3, © Springer International Publishing Switzerland 2014

Abstract The data on 6-fluoro-1,4-dihydroquinolin-4-oxo-3-carboxylic acids and their structural analogues accumulated in the literature for the last 10–15 years are reviewed. Synthetic approaches to the quinolone system, as well as all kind of structural modifications by incorporating substituents into 1–8 positions or by means of annelation have been discussed. The "structure-activity" relationships for antibacterial fluoroquinolones, as well as the data on other types of biological activity for the family of bi- and polycyclic fluoroquinolones are presented. The formation of complexes of fluoroquinolones with metals and their applications have been considered. The bibliography – 377 references.

Keywords Fluoroquinolones • Polycyclic fluoroquinolones • Synthesis • Modifications • Annelation • Activity • Metal complexes

1 Introduction

Nearly three decades passed since the time when the first representatives of the fluoroquinolone family of antibacterials, such as norfloxacin, pefloxacin, ciprofloxacin and ofloxacin had appeared in the world pharmaceutical market (Scheme 1).



Scheme 1 Structure of some fluoroquinolone antibacterials

E.V. Nosova
Department of Organic Chemistry, Chemical Technology Institute, Urals Federal University named after the First President of Russia Boris N. Yelstsin, Ekaterinburg, Russia
e-mail: emily74@rambler.ru

O.N. Chupakhin (✉)
Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, Ekaterinburg, Russia

Department of Organic Chemistry, Chemical Technology Institute, Urals Federal University named after the First President of Russia Boris N. Yelstsin, Ekaterinburg, Russia
e-mail: chupakhin@ios.uran.ru

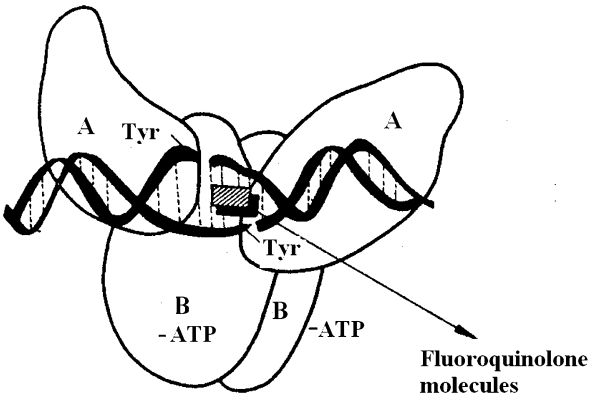


Fig. 1 Inhibiting bacterial DNA-gyrase by fluoroquinolones (Reproduced with permission of publishing Folium [6])

It is worth mentioning that the first drug in the series of quinolones, nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridin-3-carboxylic acid), bearing no fluorine atoms, was launched into medicinal practice in 1963.

Structural modification of the quinolone skeleton by incorporating of fluorine atoms at C-6 and other positions of the benzene ring resulted in a remarkable improvement of antimicrobial properties and opened new prospects in clinical treatment of infections. Indeed, compounds of the fluoroquinolone family proved to exhibit a high level of antibacterial activity and a wide spectrum which surpass many antibiotics, including the third generation of cephalosporin's and other chemotherapeutic antibacterials [1–13]. Due to enhanced penetration ability through cell membranes and their effects on bacteria reproduction by inhibiting bacterial DNA-gyrase, fluoroquinolones possess a high antibacterial activity (Fig. 1) [6].

It is extremely important that fluoroquinolones have a specific mechanism of action, different from antibiotics and other groups of antibacterials (cephalosporins, aminoglycosides, etc.), which allows one to apply fluoroquinolones for treatment of infectious diseases caused by strains resistant to many other classes of antibacterials drugs.

Depending on their behavior relative to bacteria enzymes of three types of fluoroquinolones can be distinguished:

- the first type of fluoroquinolones inhibiting mainly the topoisomerase IV: norfloxacin, enoxacin, fleroxacin, ciprofloxacin, lomefloxacin, trovafloxacin, grepafloxacin, ofloxacin and levofloxacin;
- the second type of fluoroquinolones which inhibit mainly the DNA-gyrase (nadifloxacin and sparfloxacin);
- the third type of fluoroquinolones which have a double effect: they inhibit both topoisomerase IV and DNA-gyrase: gatifloxacin, pazufloxacin, moxyfloxacin, and clinafloxacin.

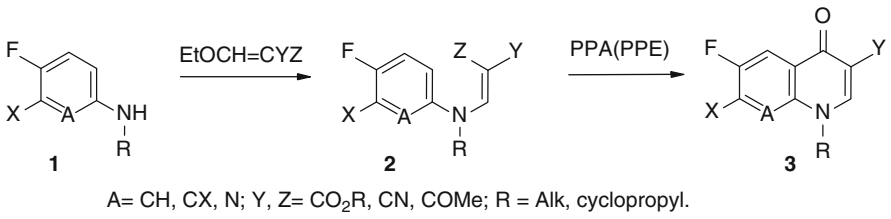
An important feature of fluoroquinolones is their selective biological action: suppressing bacterial DNA-gyrase, they don't influence the mammalian DNA cell processes. In fact, quinolones don't kill bacteria by inhibiting critical cellular processes, but rather break action of two essential enzymes, DNA-gyrase and topoisomerase IV, and use them by causing a rupture of two-spiral DNA.

During the last two decades the whole series of antibacterial fluoroquinolones have found their application in clinical practice, thus demonstrating a beginning of a new era in chemotherapy of bacterial infections. The vast majority of fluoroquinolones, launched into medical practice, are based on the bicyclic structure of 6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acid. Annelation of the benzene ring, and carbo- or heterocyclic fragments to the quinolone skeleton usually allow one to enhance antibacterial activity of fused fluoroquinolones and their therapeutical properties; in some cases derivatives of this class become capable of exhibiting other types of activity, including antiviral and antineoplastic ones. The most known representatives of tricyclic fluoroquinolones appear to be ofloxacin and levofloxacin. For many years fluoroquinolones have been intensively studied worldwide as evidenced by numerous review articles and monographs [1–13].

2 Synthesis and Antibacterial Activity of Fluoroquinolones

2.1 Bicyclic Fluoroquinolones

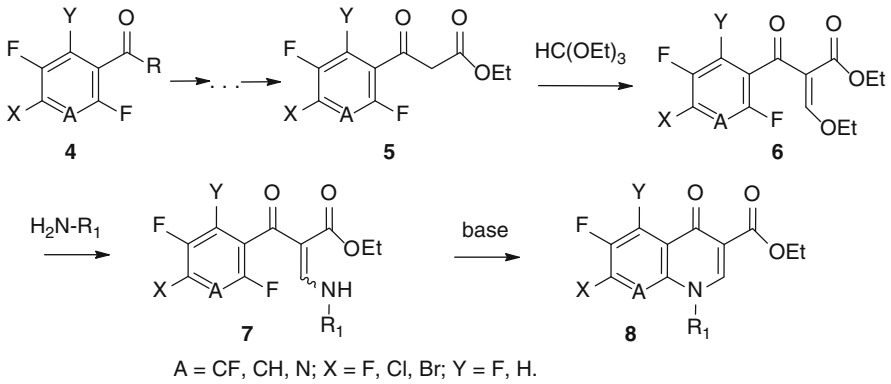
There are two basic approaches which are commonly used for the synthesis of quinolin-4-one-3-carboxylic acids [4, 14]. The first one is based on use of fluorinated anilines (**1**, A = CH, CF) or 2-aminopyridines (**1**, A = N) as starting materials and involves their condensation with ethoxymethylene derivative of malonate, cyanoacetate or acetoacetate to form enamines **2**. The intramolecular cyclization of compounds **2** with polyphosphoric acid (PPA) (the Gould-Jacobs reaction) affords the corresponding fluoroquinolones (**3**, A = CH, CF) or naphthyridones (**3**, A = N) (Scheme 2).



Scheme 2 Synthesis of fluoroquinolones from fluorinated anilines

One of the key problems of the Gould-Jacobs reaction is a choice of high-boiling solvent. Diphenyl ether which has been applied for a long time is not appropriate due to environmental reasons. A good alternative of Ph_2O seems to be a summer diesel fuel, which is cheaper than individual C_{12}-C_{18} hydrocarbons, and allows one to carry out the process at 230–245 °C providing a good purity of the key intermediates in the synthesis of fluoroquinolones.

The second approach suggests use of fluorine-containing benzoyl derivatives (**4**, A = CF, CH) or their nicotinoyl analogs (**4**, A = N) as building-blocks (Scheme 3). The key intermediates in this case are benzoyl- or pyridinoyl acrylates **6** [6]. Cyclization of enaminones **7** can be carried out by heating in DMF in the presence



Scheme 3 Synthesis of fluoroquinolones from fluorinated benzoyl derivatives

of potassium carbonate, or in ethyl acetate with NaH. Other basic conditions can also be applied, including organic amines or amidines, 1,4-diazabicyclo[2.2.2]-octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [4, 15].

The method can be improved by use of the dimethylamino analogue of intermediate **7**, which can be derived from the reaction of ethyl 3-dimethyl aminoacrylate with the corresponding fluorine-containing benzoyl chlorides followed by the displacement of the dimethylamino group with a suitable amine.

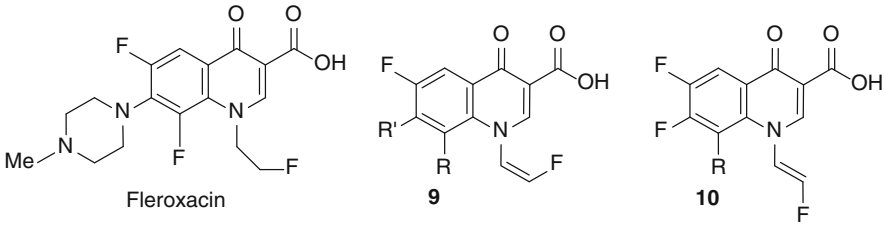
A great deal of research studies aimed at improvement of synthetic procedures leading to fluoroquinolones, enhancing their yields and quality of products, and reducing a number of steps and cost of the synthesis have been performed [16–31]. Improved synthetic procedures have been applied to obtain 1-ethyl-6-fluoro-7-(4-methylpiperazinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid and 1-ethyl-6-fluoro-7-(piperazinyl-1)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid as well as their intermediates [18–21]. Further research studies on the synthesis of more active bicyclic fluoro-quinolones to expand a range of their biological activity, and to develop antibacterial drugs against resistant strains are in progress now.

2.1.1 Modification of the Position N(1)

The nitrogen atom N-1 and N-substituents are important features of the molecule of fluoroquinolones because of their considerable contribution into antibacterial activity. Replacement of the nitrogen atom with a carbon or oxygen in analogues of the oxolinic acid results in complete deactivation of these molecules. Modification of NH fluoroquinolones is usually based on N-alkylation reaction with the corresponding alkyl halide in the presence of a base. The first representatives of commercial fluoroquinolones bearing the ethyl group at N(1) are presented by norfloxacin, pefloxacin, and enoxacin; fleroxacin has N-fluoroethyl substituent, while amifloxacin contains the N-methylamino group. Research study on activity of the series of analogues of enoxacin, bearing C_1-C_5 aliphatic groups at N(1) have shown the preference of the N-ethyl group [32].

Modification of the N-ethyl group by means of incorporation of a fluorine atom (CH_2CH_2F, fleroxacin) appeared to be a reasonable approach [33]. Also

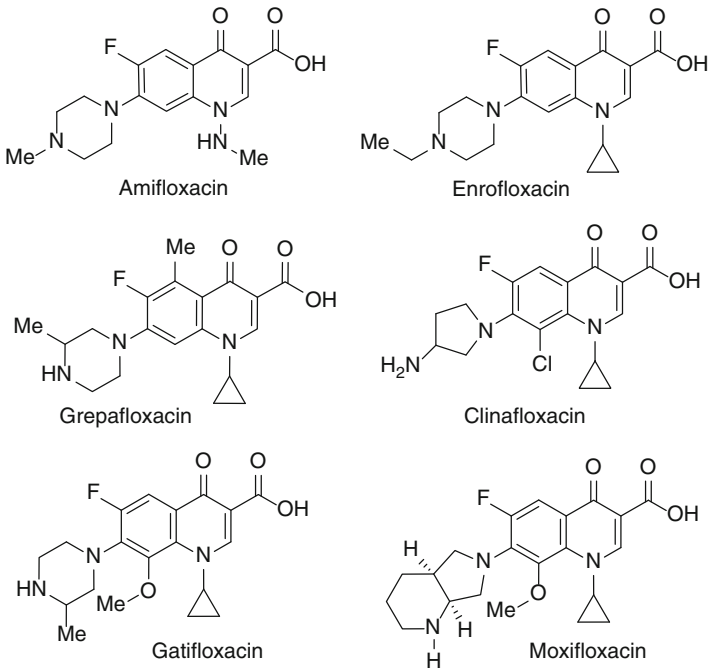
conformationally restricted analogs of fleroxacin **9** and **10** have been synthesized (Scheme 4). The *Z*-isomers proved to be 2–32-fold more potent *in vitro* against gram-positive strains of bacteria then the corresponding *E*-isomers [34].



Scheme 4 Structure of fleroxacin and analogs

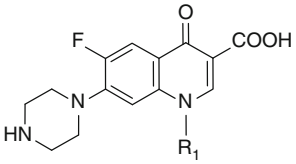
Replacement of N-ethyl group with $NHCH_3$ leads to a highly effective drug amifloxacin. Although it has not exhibited *in vitro* tests a considerable advantage in comparison with norfloxacin and pefloxacin, it shows a better pharmacokinetic profile, being equally active in both oral and parenteral administration.

It has been revealed that a high antibacterial activity of fluoroquinolones is associated with the presence of a small lipophilic group, such as, for instance, N-cyclopropyl substituent in position 1. Indeed, a number of commercially important fluoroquinolones bear the cyclopropyl fragment at N(1): ciprofloxacin, enrofloxacin, grepafloxacin, clinafloxacin, gatifloxacin, moxifloxacin (Scheme 5) [7].



Scheme 5 Structure of amifloxacin and 1-cyclopropyl-fluoroquinolones

Table 1 Activity of N(1)-substituted fluoroquinolones (MIC, μg/ml)

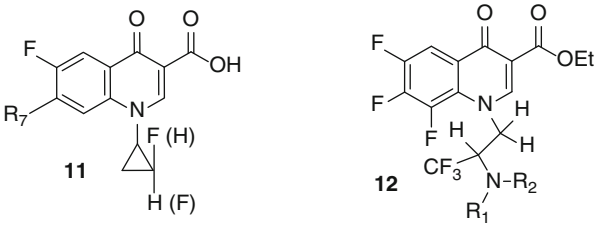


R_1	*St. aur.* A9537	*E. coli* A15119	*Ps. aer.* A 9843
Cyclopropyl (*ciprofloxacin*)	0.13	0.03	0.13
2-methylcyclopropyl (*trans*)	1	0.06	2
2-methylcyclopropyl (*cis*)	0.13	0.13	1
2,2-methylcyclopropyl	1	1	32
1-methylcyclopropyl	0.25	0.06	0.5
1-phenylcyclopropyl	0.13	0.13	4
Cyclobutyl	0.5	0.13	1

Incorporation of methyl or phenyl substituents in the cyclopropane ring, as well as the replacement of the cyclopropyl moiety with cyclobutyl or cyclopentyl ones diminishes the activity of these derivatives (Table 1) [7].

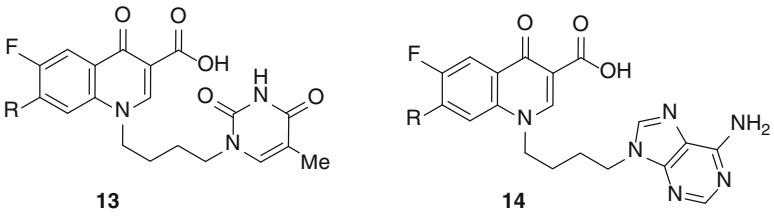
Further modification of the cyclopropyl fragment (for example, 2-fluorocyclopropyl derivatives **11**) gives rise to optically active isomers, which differ considerably in their activities, as illustrated by the fact that *cis*-analogs are more active against gram-positive strains of bacteria, than the corresponding *trans-isomers*, for example, *cis*-isomer of fluoroquinolone **11** (R_7 = 4-methyl-piperazin-1-yl) shows MIC 0,1 μg/ml against *St. aur.,* while *trans*-isomer has only 1,56 μg/ml. New synthetic approaches enabling one to introduce at N-1 of fluoroquinolones a fluorine-containing cyclopropyl fragment with a certain stereo-configuration have been developed [35, 36].

Incorporation of benzyl or *t*-butyl groups at N-1 enhances antibacterial activity of fluoroquinolones [37, 38]. Monofluoro-*t*-butyl derivatives proved to possess a higher antibacterial activity than their non-fluorinated analogs. An opportunity to use 1-trifluoromethyl-1,2-ethylenediamines for modification of position 1 of fluoroquinolones (compounds **12**) (Scheme 6) [39] has been shown.



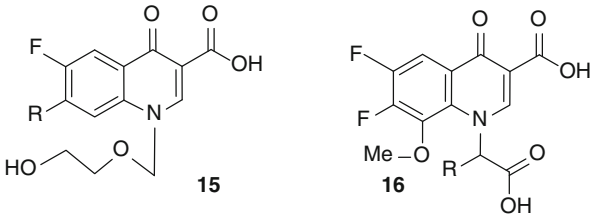
Scheme 6 Structure of fluoroquinolones **11** and **12**

Derivatives of bicyclic pefloxacin **13** and **14** represent an interesting type of hybrid molecules, in which N-butylfluoroquinolone fragments are linked with the pyrimidine and purine heterocyclic bases (Scheme 7) [40].



Scheme 7 Structure of fluoroquinolones **13** and **14**

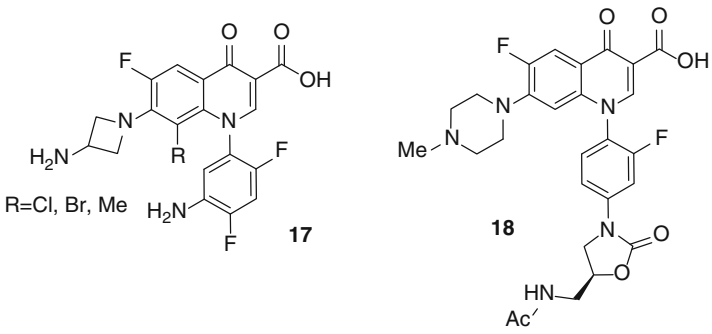
Fluoroquinolones **15** bearing the (hydroxyethoxy)methyl fragment, which is present in acyclovir, the known antiviral agent, can be regarded as acyclic analogs of nucleosides (Scheme 8) [41]. Also 5′-thioalkyl acyclic nucleosides of fluoroquinolones have been obtained by the reaction of mesylate **15** with methanethiolate- or thiophenolate anions [42].



Scheme 8 Structure of fluoroquinolones **15** and **16**

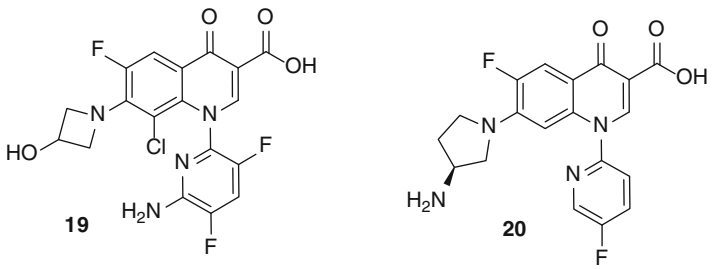
A series of new quinolones **16** bearing the fragments of natural amino acids have been synthesized. According to the data of preliminary biological studies these fluoroquinolones exhibit antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* [43].

Synthetic routes to new fluoroquinolones, containing in position 1 aryl substituent have also been described [44–46]. As a rule, a fluorophenyl substituent with one or two fluorine atoms has a favorable effect, increasing an activity of fluoroquinolones towards anaerobic bacteria. It has been found that 1-(5-amino-2,4-difluorophenyl)-8-R-substituted quinolones **17** possess a rather high antibacterial activity relative to Gram-positive and Gram-negative microorganisms (Scheme 9) [47]. 7-(Methylpiperazinyl)-6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxo-3-quinolincarboxylic acids (difloxacin) has been established to be one of the most active fluoroquinolones in experiments *in vitro* against *Chlamydia trachomatis* and other intracellular parasites; also it demonstrates excellent pharmacokinetic properties. Also, the antibacterial drug linezolid **18** bearing at N-1 2-fluoro-(4-oxazolidon-1-yl)phenyl fragment has been developed [48] (Scheme 9). N-(5-Amino-2,4-difluorophenyl)-7-aminoazetidinyl-8-chloro-substituted fluoroquinolone has been found to possess a high antibacterial activity relative to Gram-positive and Gram-negative microorganisms; its activity against *Strentococcus pneumoniae* proved to be 30-fold higher than that of trovafloxacin.



Scheme 9 Structure of fluoroquinolones **17** and **18**

A number of researches were dedicated to incorporating of heterocyclic fragments in position 1 of fluoroquinolones in expectation of enhanced activity [49]. Indeed, 1-(6-amino-3,5-difluoropyridin-2-yl) substituted quinolone **19** (Scheme 10) proved to be rather promising for treatment of serious respiratory diseases and infections of the urinary tract. This fluoroquinolone has a wide range of antibacterial activity, including quinolone-sensitive and resistant staphylococcus and streptococcus, vancomicin-sensitive and resistant enterococcus, anaerobic bacteria and other infections [50], **20** was shown to be more active than ciprofloxacin [51] (Scheme 10).



Scheme 10 Structure of fluoroquinolones **19** and **20**

1-Trifluoromethylated fluoroquinolone shows antibacterial activity at the level of norfloxacin [52]. 1-Hydroxy-2-phenyl- and 1-hydroxy-2-methyl substituted quinolones have been obtained, however they have not shown a remarkable level of antibacterial activity [53, 54].

Analysis of the data of biological trials for N-substituted fluoroquinolones available in literature enables to conclude that compounds bearing in position 1 cyclopropyl, fluorophenyl or *t*-butyl fragments exhibit a higher level of antibacterial activity than their N-unsubstituted analogues.

2.1.2 Modification of the Position C(2)

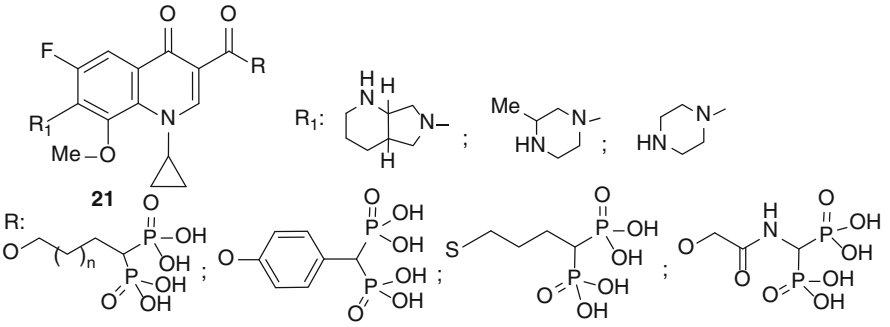
Modifications of the C(2)-position are limited due to synthetic difficulties associated with direct introduction substituents at C-2. However, the synthesis of 2-phenylsubstituted fluoroquinolones has been developed [55], and 6-fluoro-quinolon-2-carboxylic acids have been obtained by cyclization of the corresponding 2-amino-substituted 3-pentafluorobenzoyl acrylic acids [56]. 2-Thio substituted quinolones are widely used for the synthesis [*a*]- or [*b*]-annelated fluoroquinolones, such as thiazolo- and azethydinoquinolones [57–59]. Synthesis of 1-cyclopropyl-2-alkylthio-8-methoxyfluoroquinolones was described; however elucidation of their antibacterial activity revealed no regularities associated with incorporation of 2-alkylthio substituents [60]. All known 2-aza analogues of quinolones and naphthyridines, derivatives of cinnoline, have not exhibited any remarkable antibacterial activity.

2.1.3 Modification of the 3-Carboxyl Group

Modifications of the 3-carboxyl group appear to be worth only in those cases where these derivatives are considered as precursors of the corresponding carboxylic acids [61], however precursors not always exhibit activity *in vivo*. Replacement of the 3-carboxyl group with acyl, ethoxycarbonyl, methoxycarbonyl and other acidic fragments (hydroxamic, acetic, phosphonic, sulphinic or sulpho) results in complete loss or diminishes dramatically antibacterial activity of these compounds.

Functional properties of the carboxyl group have been used to modify it with osteofilic bisphosphonate fragments, as exemplified by structural modifications of moxi-, gati- and ciprofloxacin are developed [62]. Derivatives of these fluoroquinolones **21**, containing bisphosphonate ester, thioester or amide groups have been obtained (Scheme 11). Their abilities to contact bones and to recycle thus active medicinal component have been studied. It has been shown that bisphosphonate derivatives of fluoroquinolones are osteotropic predecessors for prevention of osteomielit.

Amides, hydrazides, and thiourea derivatives are important derivatives of fluoroquinolones [63–65]. It is worth noting that 7-chloroquinolones bearing



Scheme 11 Structure of fluoroquinolones **21**

the amide moiety at C-3 are rather active against *B. subtilis* and *S. aureus*. Also phenylthiourea derivatives proved to be more active against *B. subtilis* than the parent ciprofloxacin [64]. Synthesis of glycosylhydrazides and aminoacids on the basis of the corresponding hydrazido- and azido derivatives of 6-fluoroquinolin-4-one-3-carboxylic acids has been described [66].

Esters and hydrazides of 6-fluoroquinoline-4-oxo-3-carboxylic acids have been used for modification of the position 3 through the formation of heterocyclic fragments, such as oxadiazole, triazole, thiadiazole, benzofuropyrazoline, thiazolidine and others [67, 68]. Synthesis of fluoroquinolones containing in position 3 quinoxalinone, benzoxazinone and benzothiazinone fragments has recently been described [69, 70]. This synthesis was realized through interaction of fluoroquinolones bearing EtOC(O)C(O) residue with aromatic 1,2-binucleophiles. 3-Formyl- and acetyl derivatives of fluoroquinolones and also alcohols and amines have been obtained through transformation of amides [71].

It has been established that after oral administration of 3-formyl analogue of norfloxacin in mice the formyl group is metabolized rather fast into the carboxyl one, thus converting 3-formyl derivatives into norfloxacin. Due to a good solubility, a much higher level (at least two times) of the formyl derivative in blood serum can be reached, than on administration of norfloxacin, which at physiological pH values exists in the form of poor soluble zwitter-ionic form.

During the last two decades a lot of attention has been paid to development of "double mechanism" antibiotics. One of plausible approaches to such compounds is esterification of fluoroquinolone carboxylic acids with derivatives of cephalosporin and penicillin. Such combination allows one to expand a spectrum of antibacterial activity of beta-lactams conjugated with quinolones due to complementary mechanisms of their actions [7, 72].

Displacement of the carboxyl group in position 3 with hydrogen atom and the decarboxylation of fluoroquinolones have been discussed in the literature [73–76]. Since no decarboxylated fluoroquinolones have exhibited antibacterial activity, many authors have come to conclusion on the extremely importance of the 3-carboxy group.

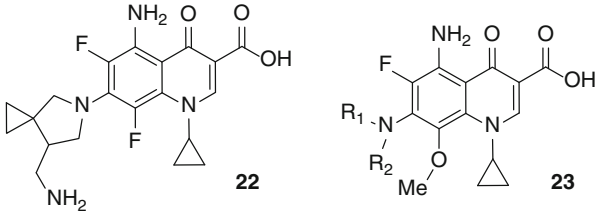
2.1.4 Modification of the 4-Oxo Group

The oxo group can be modified through the formation of oximes, hydrazones, and semicarbazones, as exemplified by transformations of norfloxacin and other fluoroquinolones [73]. Specific methods are needed to convert fluoroquinolones into their 4-alkoxy analogues, due to a preferable N-alkylation of fluoroquinolones at position 1. Another modification is the synthesis of 4*H*-1,4-benzothiazin-1-oxides and 1,1-dioxides [77] with various substituents in the benzene ring. However, these compounds proved to exhibit neither antibacterial activity, nor they inhibit DNA-gyrase. These results show that SO and SO_2 groups in quinolones cannot be regarded as bioisosters of the carbonyl group.

It has to be concluded that the oxo group at C(4) is necessary for linkage of quinolones with DNA-gyrase, and elimination or replacement of the oxo fragment with other moieties lead to inactive compounds.

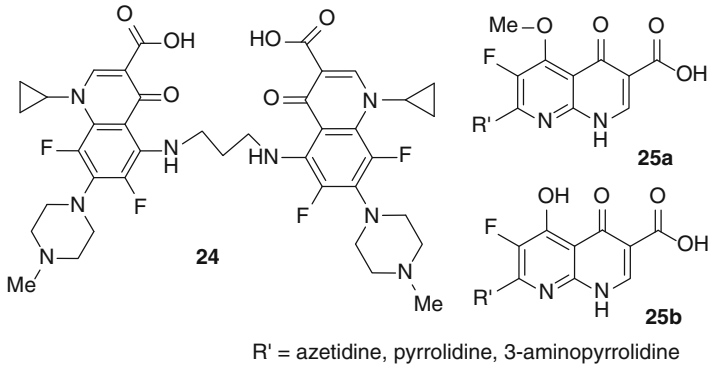
2.1.5 Modification of the Position C(5)

The most promising results have been received in those cases when the amino group was introduced at position 5 of fluoroquinolones. The detailed analysis of the "structure–activity" relationship for 5-substituted 1-cyclopropyl-6-fluoro-quinolones has shown that the positive effects of NH_2 and CH_3 groups are approximately identical, and these fluoroquinolones possess a wide range and high level of antibacterial activity [7]. Indeed, 7-(7-aminomethyl-5-azaspiro[2.4]heptan-5-yl)quinolone **22** proved to be 12 times more active against *S. aureus HPC527* than ciprofloxacin [78, 79]. The methoxy derivative **23**, and also its 8-methyl analogues show a high antibacterial activity towards a great deal of microorganisms [80] (Scheme 12). 5-Also acylaminoquinolones have been synthesized [81].



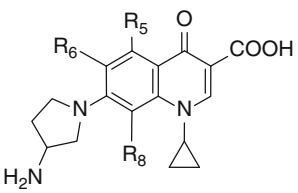
Scheme 12 Structure of 5-aminofluoroquinolones **22**, **23**

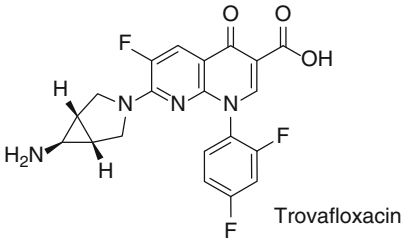
In order to obtain multi-binding therapeutic agents that modulate enzymatic processes, two fluoroquinolone ligands were linked at positions 5 through 1,3-diaminopropane bridge (compound **24**) [82]. Fluoroquinolones bearing the hydrazino group in position 5 appear to be effective antimicrobials towards a number of pathogenic microorganisms; also they possess a good solubility in water relative to other fluoroquinolones [83]. 5-Methoxy- and 5-hydroxy-6-fluoro-1,8-naphthyridin-4-oxo-3-carboxylic acids (**25a,b**) are more active against *S. pneumoniae 7257* than levofloxacin [84] (Scheme 13).



Scheme 13 Structure of fluoroquinolones **24**, **25**

Table 2 Antibacterial activity of mono- and difluoroquinolones (MIC, μg/ml)





Trovafloxacin

R^5	R^6	R^8	*St. aur.*	*E. coli*	*Ps. aer*
H	H	H	0.25	0.008	0.5
H	H	F	0.03	0.008	0.25
F	H	H	1	0.13	4
F	H	F	0.13	0.06	2
H	F	H	0.03	0.004	0.25
H	F	F	0.008	0.008	0.13

Incorporation of such substituents as Cl, Br, SH, SCH_3, CHO into position 5 of 1-cyclopropyl-6,8-difluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydro-3-quinolincarboxylic acids didn't result in substantial increase of their activity. Some substituents at C(5) have a negative effect on antibacterial activity of fluoroquinolones which can possibly be explained by steric hindrance to interaction of the 4-oxo-3-carboxy-fragment of fluoroquinolone molecules with metal ions of the bacterial DNA-gyrase. However, a fluorine atom at C-5 with nearly the same space volume as a hydrogen one also diminishes the activity of fluoroquinolones, and it can't be connected with its steric effect.

2.1.6 Modification of the Position C(6)

Replacement of a fluorine atom in position 6 with other substituents didn't enhance their activity, at the same time it was shown that in order to obtain highly active antibacterial compounds the presence of fluorine atom at C(6) is not obligatory, it is more important to have in the quinolone skeleton the N(1)-cyclopropyl and C(7)-3-aminopyrrolidinyl pharmacophoric groups (Table 2) [85–88].

Studies of antibacterial activity of 6-fluoro-1-[(*1R,2S*)-2-fluorocyclopropan-1-yl]-8-methoxyquinolones and their C(6)-defluoro analogs showed that all of them are in 4–520 times more active against gram-positive bacteria, than trova-, moxi-, gati- or ciprofloxacin [89]. These quinolones have shown the indices of activity against Gram-negative bacteria *E. coli* and *K. pneumoniae* which are comparable with those of trova- and ciprofloxacin.

Incorporation of the nitrogen atom (derivatives of 1,6-naphthiridines) proved to diminish considerably the activity of quinolones.

2.1.7 Modification of the Position C(7)

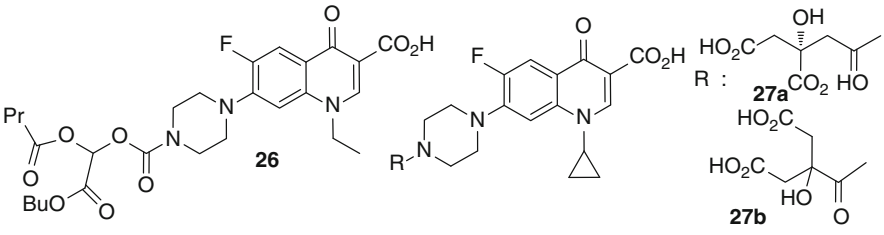
A great deal on the chemistry of 6-fluoroquinolones concerns modification of the position 7. It is due to the fact that a halogen atom at C(7) undergoes easily nucleophilic displacement with N-, S-, O- and C-nucleophiles, thus allowing one to vary the structure of quinolones. Nearly all commercially important fluoroquinolones contain at C-7 the fragments of cycloalkylimines [90–94].

Quinolones bearing in position 7 small or linear substituents, such as H, OH, OEt, COOH, Cl, Me, NH_2, NHR, NH-c-C_3H_5, $NHNH_2$, $SCH_2CH_2NH_2$ etc., have a relatively low activity against gram-positive microorganisms and are practically inactive towards the negative bacteria. Also 7-aza analogues of 6-fluoroquinolon-3-carboxylic acids, derivatives of 1,7-naphthyridines, didn't show any remarkable antibacterial activity.

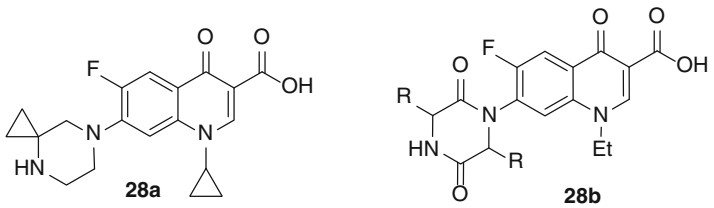
A lot of studies have been directed to the synthesis of fluoroquinolones, bearing a variety of piperazinyl substituents, since this part of quinolone molecule is of significant importance. Indeed, some representatives of 6-fluoroquinolones bearing at C(7) piperazine (norfloxacin, ciprofloxacin), 4-methylpiperazine (pefloxacin), 3-methylpiperazin (lomefloxacin, temafloxacin) proved to possess a much broader range of antibacterial activity, than those without the piperazine moiety, such as nalidixic and oxolinic acids.

In order to introduce the piperazine residue into position 7 of fluoroquinolones the reaction of 7-chloroquinolone with N-alkoxycarbonylpiperazine in high-boiling dipolar aprotic solvent followed by hydrolysis of alkoxycarbonyl group has been exploited. In some cases the borondiacetate complexes of fluoroquinolones have also been used for introduction of the piperazine fragment.

The difference in activity for *R*- and *S*-enantiomers of 7-(3-methylpiperazin-1-yl)quinolones, obtained from the corresponding (*R*)- and (*S*)-*t*-butyl-2-methylpiperazin-1-carboxylates, proved to be in the range from 2 to 64 folds in 52 % of cases [95]. In order to improve transport through biological membranes the piperazine moiety in norfloxacin was modified considerably and compound **26** was obtained [96]. To clarify the mechanism of antibacterial action of fluoroquinolones at the cellular level, two regioisomeric citrate-functionalized derivatives of ciprofloxacin **27a,b** [97] (Scheme 14) have been obtained and studied.



Scheme 14 Structure of fluoroquinolones **26**, **27**

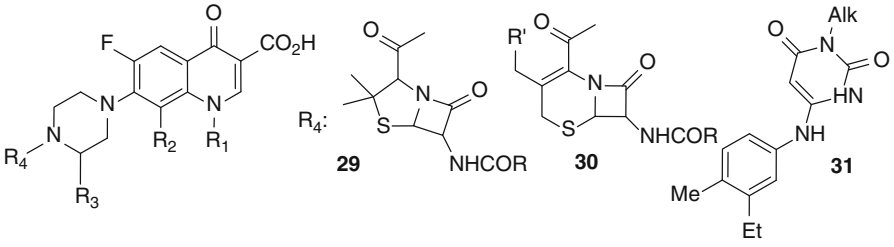


Scheme 15 Structure of fluoroquinolones **28**

Introduction of spiropiperazine or piperazinedione groups in position 7 of 1-cyclopropyl substituted fluoroquinolones has been shown to enhance their antimicrobial activity (compounds **28a,b**) (Scheme 15) [98, 99].

Also the piperazine fragment of fluoroquinolones was modified by introduction of a number of heterocyclic fragments, such as 2,6-diaminopyrimidinyl, 4,6-diamino-1,3,5-triazinyl, 2-aminothiazinyl, 1,3,4-thiadiazolyl, 2-furyl and other groups, thus allowing one to obtain more active antibacterial drugs [100–103].

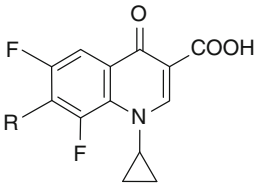
Hybrid derivatives of fluoroquinolones bearing fragments of penicillin and cephalosporin antibiotics or uracils, for example compounds **29–31**, proved to possess a wide spectrum and high level of antibacterial activity, including their potency against resistant to β-lactams strains [74, 104–107] (Scheme 16). High antibacterial activity has also been shown by 7-(N-aryl-2,2,2-trifluoroacetimidoyl)piperazinyl derivatives of fluoroquinolones [108].



Scheme 16 Structure of fluoroquinolones **29–31**

Influence of the second heteroatom in the piperazine ring is not so unequivocal. For instance, the replacement N(4) in the piperazine moiety of amifloxacin with O, S or CH_2 fragments has been shown to diminish activity of these compounds *in vitro* and *in vivo*, however when the piperazine residue in norfloxacin was replaced with thiomorpholine a much more potent compound against Gram-positive bacteria has been obtained. 7-(3-Aminomorpholin-1-yl) and 7-[3-(or 4)-aminomethylpiperidin-1-yl]-derivatives proved also to possess a high activity against St. aur. (Table 3). 7-Azetidinyl substituted fluoroquinolones, in particular *trans*-3-amino-2-methyl-1-azetidinyl derivatives proved to be highly active antibacterial compounds [84, 109, 110].

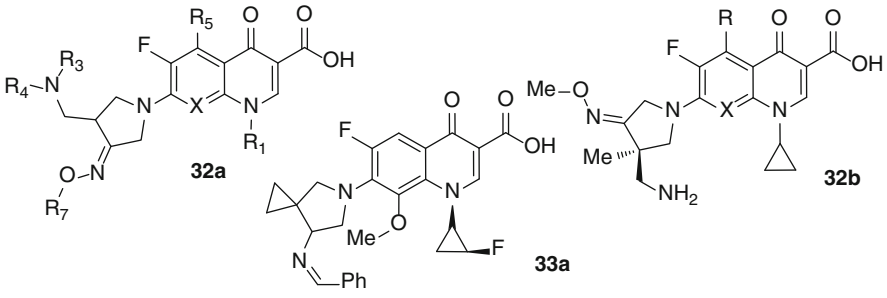
Table 3 Antibacterial activity of 7-substituted fluoroquinolones (MIC, μg/ml)



R	*St.aur.*	*E. coli*	*Ps.aer.*
Piperazin-1-yl	0.10	0.006	0.10
Piperidin-1-yl	0.78	3.13	50
Morpholin-1-yl	0.025	0.10	0.78
3-Aminomorpholin-1-yl	0.025	0.10	0.78
3-Methylaminomorpholin-1-yl	0.025	0.10	3.13
3-Acetylaminomorpholin-1-yl	0.20	1.56	12.5

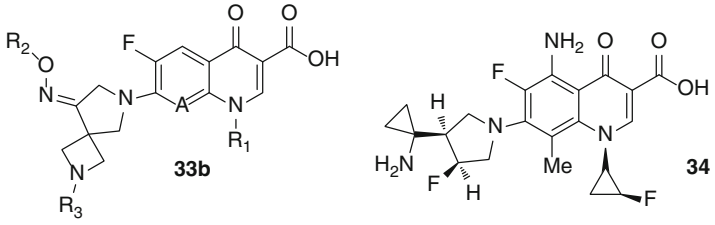
A large group of highly active fluoroquinolones contains the pyrrolidine fragment in position 7, and, therefore, a considerable attention has been paid to the synthesis of 6-fluoro-7-pyrrololidinoquinolones with 3-amino-, 3-aminomethyl- or 3-(2-cyanomethylamino) substituents in the pyrrolidine ring [111–114]. As a rule, the compounds of this series possess a much higher activity towards Gram-positive microorganisms than the corresponding piperazine derivatives.

Fluoroquinolones **32a**, containing alkyloximino substituent at C-4 and the aminomethyl fragment at position 3 of the pyrrolidine ring, exhibit a high antibacterial activity towards Gram-positive and Gram-negative microorganisms, including a methicillin-resistant strain of *S. aureus* (MRSA) [115–118]. Compounds **32b** having an optically active center in the pyrrolidine ring and the methyloximino group proved to possess not only high antibacterial activity, but also a good pharmacokinetic profile [119, 120]. Also, the series of fluoroquinolones, containing spiropyrrolidine substituents at C-7, for example, compound **33a**, have been obtained (Scheme 17) [121, 122].



Scheme 17 Structure of fluoroquinolones **32, 33a**

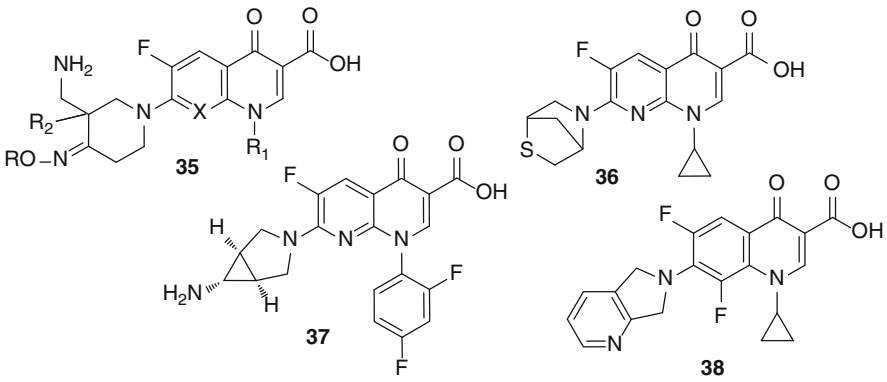
Effects of the chiral fragments, such as 1-(*cis*-2-fluorocyclopropyl) and 7-(7-amino-5-azaspiro[2.4]heptyl) substituents (compounds **32b, 33a**) on antibacterial properties of the series of fluoroquinolones have been studied (Scheme 18) [123]. It has been shown that derivatives of 1-[(*1R,2S*)-2-fluorocyclopropyl]- and 7-[(*7S*)-amino-5-azaspiro[2.4]heptyl]-fluoroquinolones are more active towards a number of Gram-positive and Gram-negative bacteria, than other stereoisomers. The presence of spiropyrrolidine residue at C(7) of fluoroquinolones enhances their lipophilic properties, thus promoting a better assimilation on oral administration [98].



Scheme 18 Structure of fluoroquinolones **33b, 34**

Compounds **33b, 34** with the amino group attached to the spiropyrrolidine or cyclopropyl-substituted pyrrolidine fragment proved to exhibit broad spectrum of antibacterial activity (Scheme 18) [124–129]. Aminomethyl substituted pyrrolidines and their heterocyclic derivatives were incorporated into position 7 of fluoroquinolone [130–132]. Optically active derivatives of 7-(3-hydroxypyrrolidin-1-yl)-6-fluoroquinolones have been shown to be promising antibacterials [133–135].

One more residue which is frequently present in position 7 of active fluoroquinolones is piperidine [136–139]. Indeed, 1-cyclopropyl-6-fluoro-quinolones, containing (*3S*)-amino-(*4R*)-piperidinyl fragment in position 7, show a high activity towards resistant strains of *Staphylococus aureus* and *Streptococus pneumoniae* [140]. A number of substituents, such as 4-amino, 4-hydroxy, 3-aminomethyl, 4-aminomethyl and 3-methylamino were incorporated in the piperidinyl fragment [141, 142]. Novel 6-fluoroquinolones and naphthyridines with 4 (3)-alkoxyimino-3-aminomethyl-3-H(methyl)piperidinyl substituents, for instance **35**, have been obtained (Scheme 19) [143–145]. They shown a high activity against all gram-positive organisms, including those resistant to fluoroquinolones. One of compounds of this series proved to be in 16–128, 2–32 and 4–8 times more active against fluoroquinolone-resistant MSSA, MRSA and MRSE than gemi-, cipro- and levofloxacin, respectively. Introduction of 4-(1*H*-1,2,3-triazol-1-yl)piperidinyl residue in the structure of fluoroquinolone resulted in a good activity against *S. aureus* and *S. epidermidis* [146].

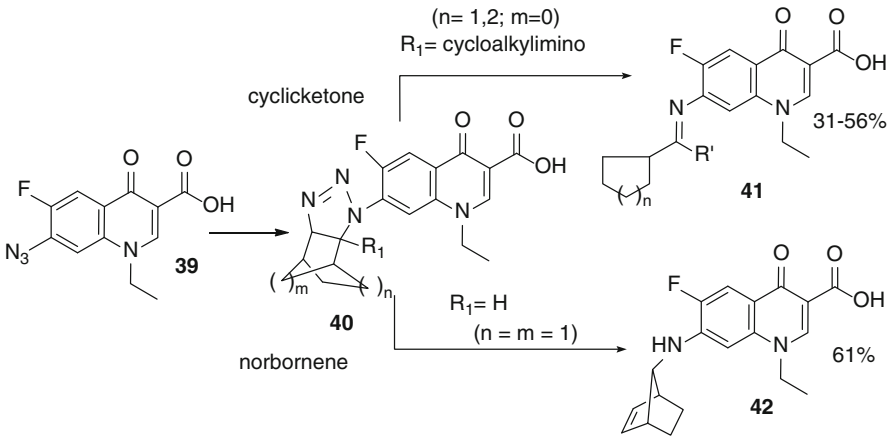


Scheme 19 Structure of fluoroquinolones **35**–**38**

A very promising modification of fluoroquinolones is introduction of bridged cyclic amines in position 7 [147–153]. A series new fluoroquinolones **36** was synthesized (Scheme 19), and one of compounds showed high activity against quinolone-sensitive and multi-resistant bacteria, especially towards *Streptococcus pneumonia* [154].

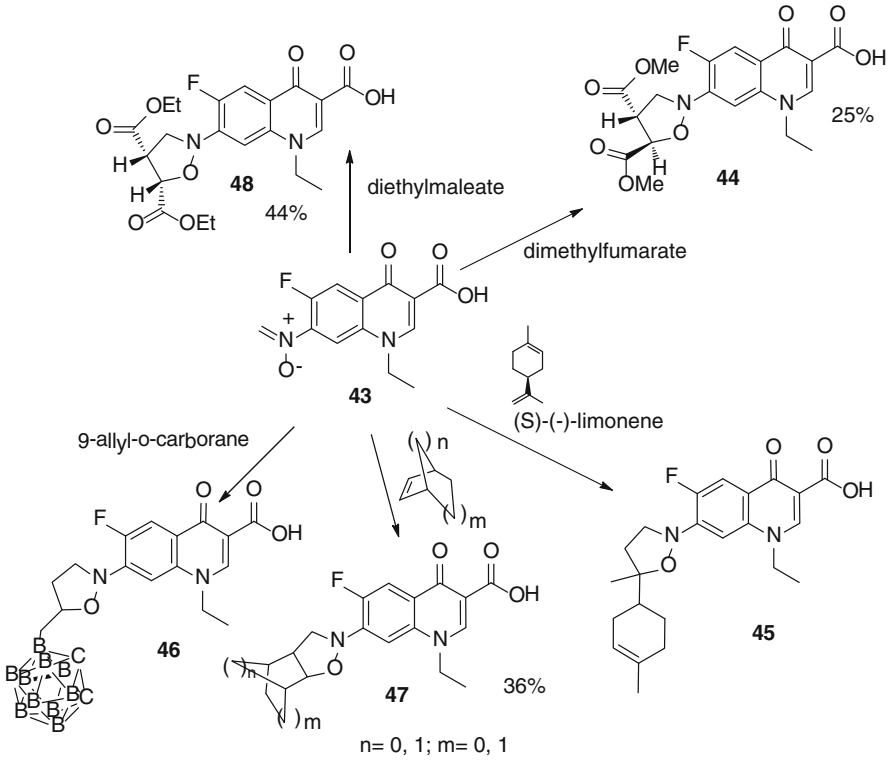
Trovafloxacin **37**, the very active compound with a wide spectrum of action, contains 7-(1α, 5α, 6α)-3-azabicyclo[3.1.0]hexyl substituent (Scheme 19) [155, 156]. 6-Fluoro-1-[(*1R, 2S*)-2-fluorocyclopropan-1-yl]-4-oxoquinolin-3-carboxylic acids, containing in position 7 2-amino-8-azabicyclo[4.3.0]nonan-8-yl fragment have been shown to inhibit bacterial DNA topoisomerase IV very effectively [157]. A great deal of research are dedicated to the synthesis and biological tests of 7-di- and triazabicyclononyl substituted 6,8-difluoroquinolones, for instance **38** (Scheme 19) [158–163].

An effective way for introduction of a variety of heterocyclic fragments in the position 7 of the fluoroquinolone skeleton is the methodology of 1,3-dipolar cycloaddition reactions [164–167]. Indeed, the reaction of 7-azido derivative of 6-fluoroquinolone **39** with enamines of cyclic ketones and norbornene proceeds rather smoothly with the formation of the corresponding *exo*-1,2,3-triazolines **40** which undergo the cationic rearrangements into amidines **41** or aminonorbornane **42** [164, 165]. 7-Azido derivatives **39** are capable of reacting with heterocyclic amines to form new 7- fluoroquinolones (Scheme 20) [168].



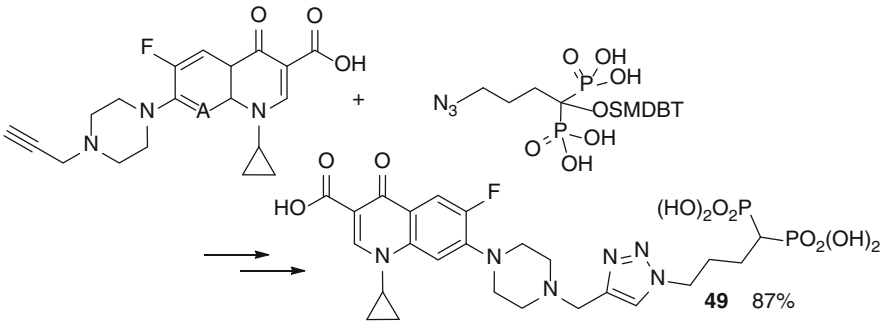
Scheme 20 1,3-Dipolar cycloaddition reactions of 7-azido derivative **39**

The cycloaddition reaction of azomethine **43** with alkenes proceeds in regio- and stereoselective manner and represents a convenient way to obtain a variety of stereoisomeric 7-isoxazolidinyl quinolones **44–48** [166, 167] (Scheme 21).



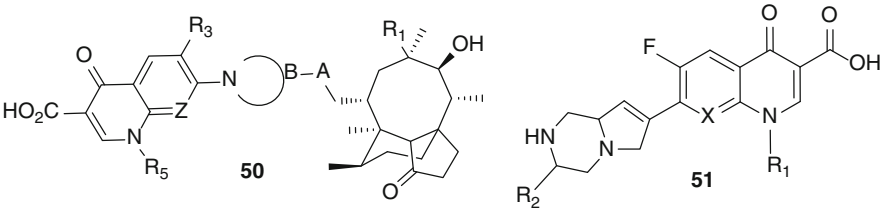
Scheme 21 The cycloaddition reactions of azomethine **43**

Synthesis of new hydroxybisphosphonate derivatives of ciprofloxacin **49** has been performed by using Cu-catalyzed 1,3-dipolar cycloaddition reaction between the corresponding azide and N-alkynyl substituted quinolone [169] (Scheme 22). Derivatives of gati- and moxifloxacin have been obtained similarly. All of these modified compounds maintained antibacterial activity of the starting quinolones and, in addition to that, exhibit osteotropic properties.



Scheme 22 Synthesis of fluoroquinolone **49**

A number of 6-fluoroquinoline- and 6-fluoronaphthyridine-3-carboxylic acids, containing at C(7) rather complicated fragment of multiline (compounds **50**) have been synthesized (Scheme 23) [170]. Quinolones **50** exhibit a high activity against resistant bacteria, in particular, methicillin- and quinolone-resistant *Staphylococcus, Streptococcus pneumoniae*, etc.



Scheme 23 Structure of fluoroquinolones **50**, **51**

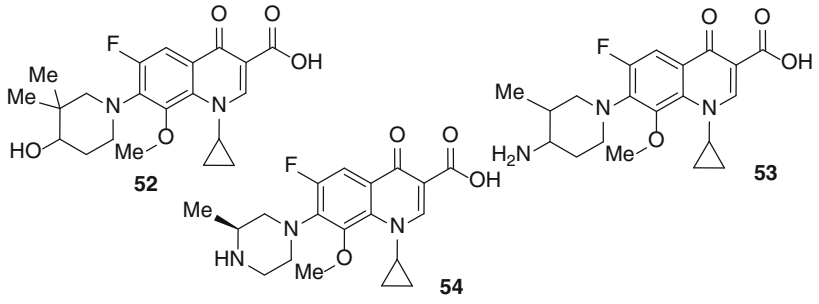
Synthesis on the basis of organoelement compounds play an important role for modification of position 7 in fluoroquinolones [171]. As mentioned above, fluoroquinolones, containing hetaryl residues in position 7 are promising for medicinal chemistry [172]. In particular, a number of highly active fluoroquinolones have been obtained on the basis of 7-nitromethyl derivatives [173, 174].

The 7-(1,2,3,4-tetrahydropirrolo[1,2-*a*]pyrazin-7-yl) fragment has been incorporated in the structure of quinoline and naphthiridine carboxylic acids **51** through the carbon-carbon bond formation by reacting 7-halogeno or tosyl-substituted quinolones with the corresponding borates (Scheme 23) [175]. It should be noted that several compounds of this series have exhibited a high activity against ciprofloxacin-resistant bacteria of *Streptococcus pneumoniae*.

Thus, varying substituents in position 7 provides a good platform for development of novel antibacterial drugs. New opportunities for modification of position 7 are associated with design of hybrid molecules, as illustrated, for instance, by the development of the double action drugs containing both a fluoroquinolone and β-lactam antibiotic fragments.

2.1.8 Modification of Position C(8)

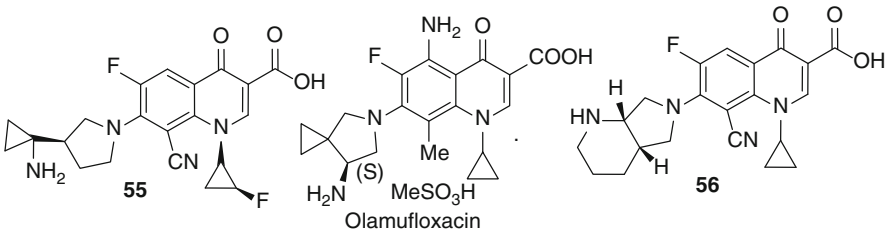
The nature of substituents in position 8 of fluoroquinolones also makes a certain impact on antibacterial activity. The key role of the 8-methoxy substituent is demonstrated by the fact that this fragment is a part of such effective drugs, as moxifloxacin and gatifloxacin [176–180]. Indeed, fluoroquinolone **52** shows a high activity against *H. influenza* and *M. catarrhalis* [181], while compound **53** is 4 times more active against *S. pneumoniae* than levofloxacin [182, 183]. 8-Methoxy-6-fluoroquinolone **54** has smaller side effects on the cardio-vascular system, than gatifloxacin (Scheme 24) [184].



Scheme 24 Structure of fluoroquinolones **52**–**54**

Fluoroquinolones, containing 8-methyl substituent usually demonstrate a high antibacterial activity, e.g. olamufloxacin is of great importance for treatment of urological diseases [185–188]. Also the cyano group in position 8 proved to be an appropriate substituent, as illustrated by the synthesis of 8-cyanoquinolones **55** and **56** [189] (Scheme 25). Indeed, compound **55** has been shown to possess a high antibacterial activity towards Gram-positive and Gram-negative bacteria [193], while 8-cyanoquinolone **56**, containing the diazobicyclononane residue in position 7 is more active antibacterial compound than enrofloxacin (Scheme 25) [190].

Substituents NO_2, NH_2, SCH_3, CF_3 in position 8 have usually a negative impact on both *in vitro* and *in vivo* activities, especially towards Gram-negative microorganisms.

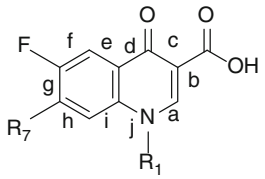


Scheme 25 Structure of olamufloxacin and fluoroquinolones **55**, **56**

In order to obtain "structure-biological activity" relationships mathematic methods have been used [191–193]. Quantitative correlations between molecular structure and pharmacokinetic and pharmacodynamic characteristics of fluoroquinolones in combination with informative hemometric approach have been used to forecast anti-pneumococcus activity [194]. Elucidation of the structure – activity relationships in the series of fluoroquinolones is the subject of numerous publications [195–197]. Dependence of antibacterial activity on the nature of substituents has been established for several series of bicyclic fluoroquinolones [11, 198–200].

2.2 Polycyclic Fluoroquinolones

Modification of fluoroquinolones by annelation of carbo- or heterocyclic rings leads to fused polycyclic systems (Scheme 26).

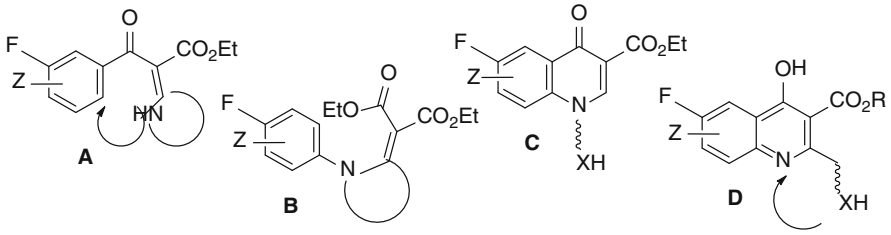


Scheme 26 Possible locations of additional rings in polycyclic fluoroquinolones

2.2.1 [*a*]-Annelated Fluoroquinolones

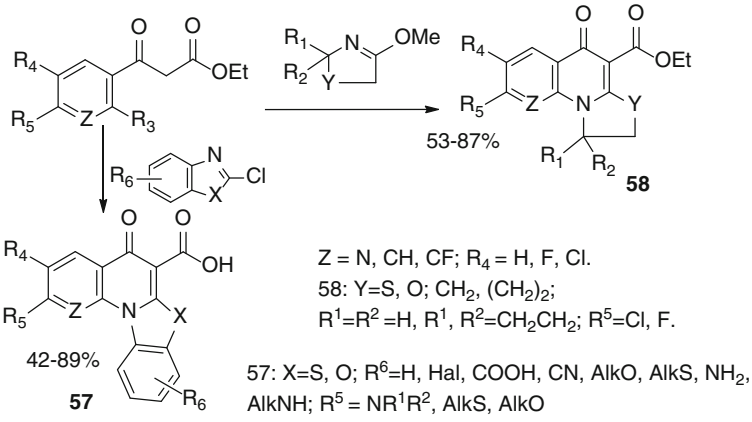
There are two principal approaches to the synthesis of [*a*]-annelated fluoroquinolones. The first one suggests that an [*a*]-annelated ring is already involved in the structure of intermediates, such as aminoacrylates A or malonates B, followed

by their cyclization into the corresponding fluoroquinolones. The second approach is based on use of 1- or 2-substituted quinolones C or D, which undergo intramolecular [*a*]-fusion (Scheme 27) [10].



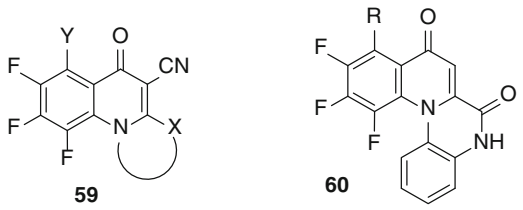
Scheme 27 Approaches to the synthesis of [*a*]-annelated fluoroquinolones

The first approach has been used to obtain [*a*]-annelated fluoroquinolones **57** and **58** from the correspondingly substituted ethyl acetates and 2-chlorobenzazoles or iminoesters (Scheme 28). 7-(1-Piperazinyl)- and 7-(4-methyl-1-piperazinyl)-benzothiazolo-[3,2-*a*]quinolones **57** have been established to exhibit rather good activity against a number of bacteria [201].



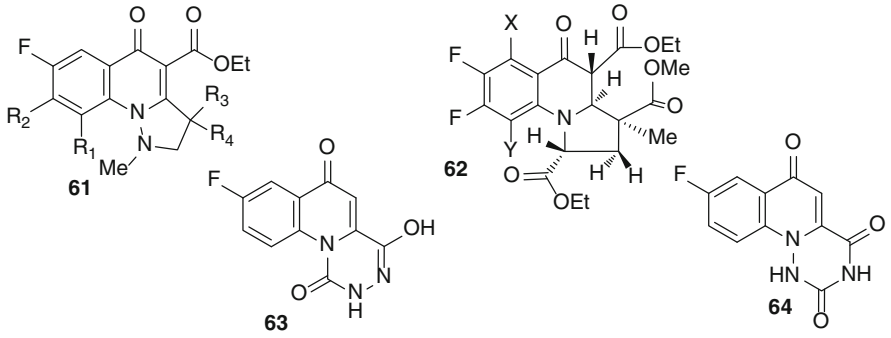
Scheme 28 Synthesis of azolo[*a*]quinolones

Synthetic routes to [*a*]-fused quinolones of general formula **59** from the corresponding polyfluorobenzoyl chlorides and α-azahetaryl acetonitriles have been developed [202]. Heterocyclization of quinoxalones, containing polyfluoroaroyl fragment in position 3 in DMSO in the presence of triethylamine affords **60** (Scheme 29) [203].



Scheme 29 Structure of fluoroquinolones **59**, **60**

The [*a*]-annelation in which the starting material is N-methylaminoquinolone has been described [204, 205]. Use of the 1,4-addition to the activated multiple bonds followed by the Michael intramolecular reaction leads to tetrahydropyrazolo[1,5-*a*] quinolones **61**, which are oxidized into the corresponding pyrazolo[1,5-*a*]quinolones. Hexahydropyrrolo[1,2-*a*]quinolones **62** can be regarded as [3+2] adducts derived from the reactions of N-(ethoxycarbonyl)methyl substituted ethyl esters of di-, three- and tetrafluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acids with methylmetacrylate (Scheme 30) [206].

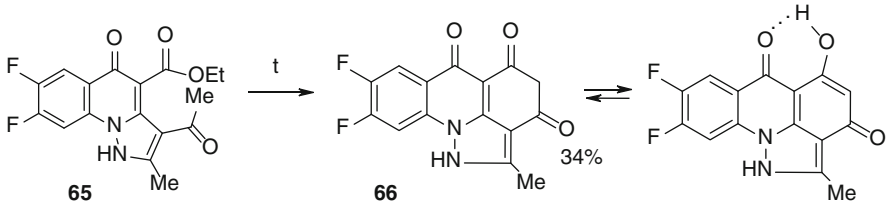


Scheme 30 Structure of fluoroquinolones **61**–**64**

Derivative of [1, 2, 4]triazino[1,6-*a*]quinoline **63** has been obtained from methyl 6-fluoro-4-oxo-1,4-dihydro-2-quinolincarboxylate through the N-amination followed by condensation of the corresponding aroyl isocyanate and cyclization of the obtained α-semicarbazidocarboxylate [207]. 8-Fluoro-4-hydroxy-*1H*-[1,2,4]-triazino[4,5-*a*]-quinolin-1,6(*2H*)-dione **64** has been obtained by condensation of 6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarbohydrazide by action of phosgene [208]. 8-Fluoro-1,2-dihydro[1,4]oxazino[4,3-*a*]quinolin-4,6-dione was derived from intramolecular cyclization of 2-chloroethyl 6-fluoro-4-oxo-1,4-dihydro-2-quinolincarboxylate [209]. New tetracyclic system containing fluoroquinolone fragment **66** was obtained by intramolecular condensation of ethyl 3-acetyl-5-oxopyrazolo[1,5-*a*]quinolin-4-carboxylate **65** on heating [210] (Scheme 31).

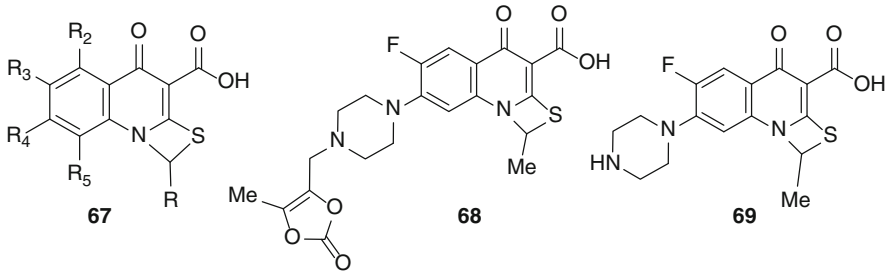
Table 4 Activity of **67** (R = Me, $R^2 = R^5 = H$, $R^3 = F$), MIC, μg/ml

R^4	*St. aur.*	*E. coli*	*Ps. aer.*
Piperazinyl	0.05	0.0125	0.2
4-Methylpiperazinyl	0.1	0.025	0.39
Morpholinyl	0.1	0.1	0.39
Thiomorpholinyl	0.025	0.2	0.39



Scheme 31 Synthesis of tetracyclic fluoroquinolone **66**

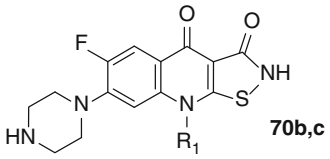
2-Mercapto-6-fluoroquinolin-3-carboxylic acids are considered as important intermediates in schemes leading to [*a*]-annelated fluoroquinolones, as shown by the synthesis of a number of thiazeto[*a*]quinolones **67** possessing a high level of antibacterial activity (Table 4) [211–213]. For instance, modification of position 7 of thiazeto[3,2-*a*]quinolones results in the formation of highly effective tricyclic antibacterials, such as prulifloxacin **68**, which is metabolized in organisms into ulifloxacin **69** (Scheme 32) [214–217]. It is worth noting that decarboxylation of ulifloxacin drops down the antibacterial activity in 60–12,000 times. A similar phenomenon has been observed in case of cipro- and moxifloxacin [60], thus showing an extremely important role of the carboxyl group. The synthesis of thiazolo[3,2-a]-, [1,3]benzothiazino[3,2-*a*]- and [1,3]benzothiazino[1,2-*a*]quinolin-6-carboxylic acids has also been reported [218, 219].



Scheme 32 Structure of thiazeto[*a*]quinolones **67–69**

It should be noted that [*a*]-annelation of additional rings through the reactions of1- or 2-substituted fluoroquinolones has certain restrictions, while cyclocondensation of fluorinated benzoyl chlorides with C,N-bifunctional nucleophiles appears

Table 5 Antibacterial activity of [*b*]-annelated fluoroquinolones (MIC, μg/ml)



70b,c

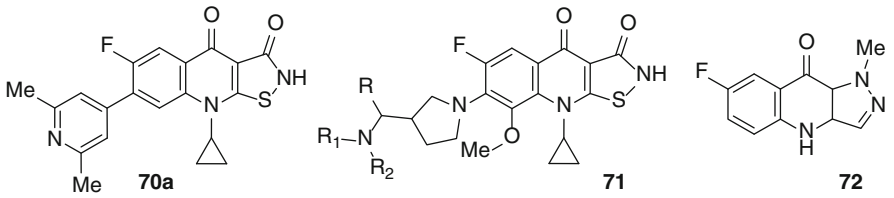
Compound	*St. aur.*	*E. coli*	*Ps. aer.*
70b (R^1 = ethyl)	0.02	0.005	0.05
Norfloxacin	0.20	0.01	0.1
70c (R^1 = cyclopropyl)	0.1	0.1	0.20
Ciprofloxacin	0.78	0.1	0.39

to be a more common method for the synthesis of a broad range of [*a*]-annelated fluoroquinolones. Incorporation of original bicyclic amines at position 7, as well as the synthesis of new derivatives through reactions of the carboxyl group are the main directions for modification of [*a*]-annelated fluoroquinolones.

2.2.2 [*b*]-Annelated Fluoroquinolones

The thesis concerning necessity of the carboxyl group in position 3 of fluoroquinolones to provide their antibacterial properties is not in agreement with the data on activity of [*b*]-annelated isothiazolo-, pyrido-, pyrimido- and pyrazinoquinolones which stimulated research studies of this group of compounds [7]. Indeed, a whole number of oxoisothiazolo[5,4-*b*]quinolones possessing a high antibacterial activity (Table 5), for instance compound **70a** and its analogues, have been obtained [220–224]. Also 9-cyclopropyl-6-fluoro-8-methoxy-7-(2-methylpyridin-4-yl)-9*H*-isothiazolo[5,4-*b*]-quinolin-3,4-dione has shown a high activity *in vitro* against methicillin-sensitive strains of *Staphylococcus aureus* (MRSA), high level of inhibiting of DNA-gyrase and topoisomerase IV of *S. aureus*, in combination with a neglect able effect on human topoisomerase II and low cytotoxicity [225, 226]. A series of 7-(3′-substituted) pyrrolidinyl-8-methoxyisothiazolo[*b*] quinolones **71** has been obtained and their antibacterial activity towards methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli*, including stereochemical aspects and influence of substituents, has been elucidated [226].

The synthesis of 1-methyl-1,4-dihydro-9H-pyrazolo[4,3-*b*]quinoline-9-one **72,** inhibitor of protein kinase C, has been performed by means of cyclization of 4-[(4-fluorophenyl)amino]-1-methyl-1H-pyrazole-5-carboxylic acid (Scheme 33) [227]. The main trends in development of research studies in the field of [*b*]-annelated fluoroquinolones are dealt with use of these compounds for the synthesis of novel [*i,j*]-annelated systems, a varying of substituents at C-7, and also with obtaining of new 2-substituted fluoroquinolones.



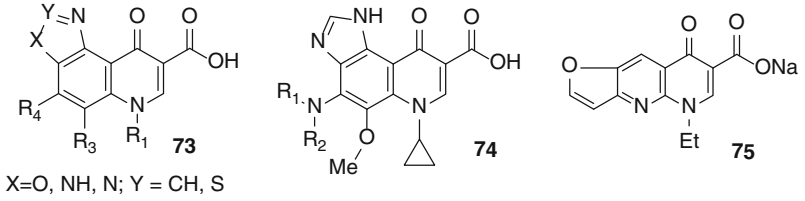
Scheme 33 Structure of [*b*]-annelated quinolones **70a-72**

2.2.3 [*c*]- and [*d,e*]-Annelated Fluoroquinolones

The targeted synthesis of these types of fused fluoroquinolones has never been carried out, since the oxo-group in position 4 which is responsible for linkage of fluoroquinolones with DNA gyrase has to be eliminated [7].

2.2.4 [*f*]- and [*g*]-Annelated Fluoroquinolones

Both [*f*], and [*g*]-annelation results in loss of fluorine atom in position 6 the presence of which has long been associated with a high level of antibacterial activity of fluoroquinolones. However, a number of highly active compounds have been revealed in the series of oxazolo-, thiazolo- and imidazo[4,5-*f*] fused fluoroquinolones. For instance, derivative **73** ($R^3 = R^4 = F$) has shown a good activity against both Gram-positive, and Gram-negative bacteria [228]. According to *in vitro* biological tests 5-methoxyimidazo[4,5-*f*]quinolones **74** exceeds in activity the corresponding analogs of ofloxacin [229]. Furonaphthyridine **75** has found application as the basis to obtain antibacterials (Scheme 34) [230].



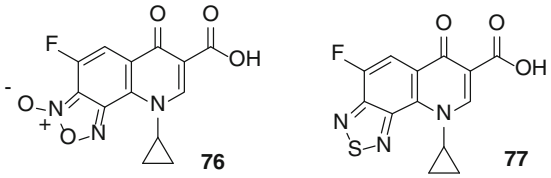
Scheme 34 Structure of [*f*]-and [*g*]-annelated fluoroquinolones **73–75**

2.2.5 [*h*]-Annelated Fluoroquinolones

6-Oxo-6,9-dihydro[1,2,5]oxadiazolo[3,2-*h*]quinolin-7-carboxylic acid **76** was synthesized from 7-azido-8-nitroquinolone [231]. A convenient method for the synthesis of 6-oxothiazolo[3,4-*h*]quinolin-7-carboxylic acids 77 has been suggested (Scheme 35) [232]. The structure of compounds **76** and **77** has been confirmed by X-ray crystallography. Biological tests of fluoroquinolone **77** have revealed that this compound possesses a high activity against Gram-positive *bacilli* and *staphylococci*, including methicillin-resistant strains, as well as Gram-negative bacteria (Table 6).

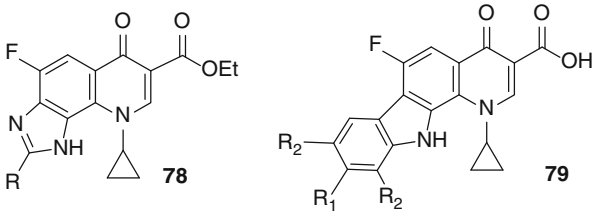
Table 6 Activity of **77** (MIC, μg/ml)

Compound	*Bacillus cereus*	*Bacillus subtilus ATCC 6633*	*Methicillin-resistant S. aureus*	*E. coli* ATCC8739
Ciprofloxacin	0.15	0.03	0.7	0.015
77	0.15	0.07	1.5	0.7



Scheme 35 Structure of [*h*]-annelated fluoroquinolones **76**, **77**

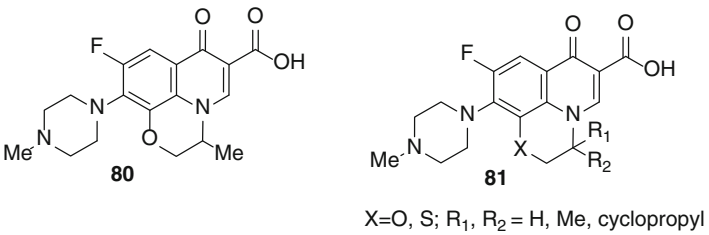
A series of ethyl 2-R(Ar)-9-cyclopropyl-4-fluoro-6-oxo-1H-imidazo[4,5-*h*] quinoline-7-carboxylates **78** have been obtained through cyclocondensations of the corresponding 7,8-diamino quinolones [233]. Also a number of tetracyclic [*h*]-annelated fluoroquinolones, such as 1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-*a*]carbazole-3-carboxylic acids **79** and their thiene isosters have been obtained (Scheme 36) [198]. All derivatives proved to possess a high activity against *Bacillus subtilus* and *Staphylococci*.



Scheme 36 Structure of [*h*]-annelated fluoroquinolones **78**, **79**

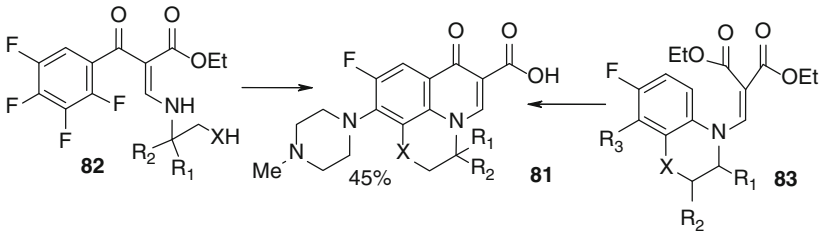
2.2.6 [*i,j*]-Annelated Fluoroquinolones

The most known representatives of tricyclic [*i,j*]-annelated fluoroquinolones are **ofloxacin 80** and its analogues **81** (Scheme 37) [234]. Ofloxacin is well-known to clinical physicians, since more than 15 years it has been applied in medical practice. Ofloxacin has produced in two ready forms, peroral and injective ones, and both of them are characterized by a high clinical efficiency, wide range of indications for treatment, relative stability of the ofloxacin molecule in the process of bio-transformations in organism, and a low interference with drugs of other pharmacological groups. The oxygen atom in the oxazine ring is supposed to be an important element of the structure, thus providing an optimal antibacterial effect of this compound. Ofloxacin represents a racemic mixture of the right- and left-rotating optical isomers. The left-rotating enantiomer, levofloxacin, which proved to be much more active than its stereo analogue against nearly all bacteria, had been launched into medicinal practice in 1997. Inhibition of *E. coli* DNA gyrase by levofloxacin (I_{50} 2,50 μg/ml) was shown to surpass inhibition of the same enzyme by ofloxacin (I_{50} 6,20 μg/ml) [235].



Scheme 37 Structure tricyclic [*i,j*]-annelated fluoroquinolones

The starting materials **82** for the synthesis of ofloxacin and its analogues have been obtained by interacting ethyl 2-(tetrafluorobenzoyl)-3-ethoxy acrylates with 2-aminopropanol [236]. It is clear that use of optically active *S*-(-)-2-aminopropanol enables one to obtain levofloxacin [237–241]. Another approach to fluoroquinolones **81** is cyclization of compounds **83**, derived from condensation of the corresponding benzoxa(thia)zines with diethylethoxy methylenemalonate (Scheme 38). In this way the synthesis of levofloxacin has been realized from the (*S*)-isomer of 7,8-difluoro-2,3-dihydro-3-methyl-4H[1, 4]benzoxazine [242].

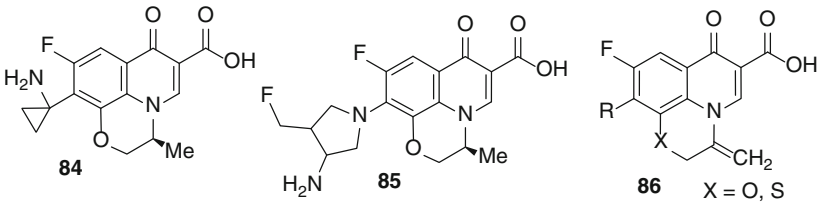


Scheme 38 Synthesis of fluoroquinolones **81**

During the last two decades the synthesis of levofloxacin and its *S*-(-)-precursors has been improved considerably, and new approaches have been advanced [243–255]. In particular, kinetic resolution of 7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]-benzoxazine racemate using naproxen, N-[sulphonylsubstituted]-(*R*)-proline and (*2S*)-(6-methoxynapht-2-yl)propionyl chloride, has been advanced [256–261]. The optically active (*S*)-isomer obtained by this method has been used for the synthesis of levofloxacin (*S*)-(-)-**80** [256]. Also a new synthetic approach to (*S*)-isomer through catalytic reduction of 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine with use of chiral Bronsted acids as catalyst and substituted dihydropyridine as a source of hydrogen has been described [262].

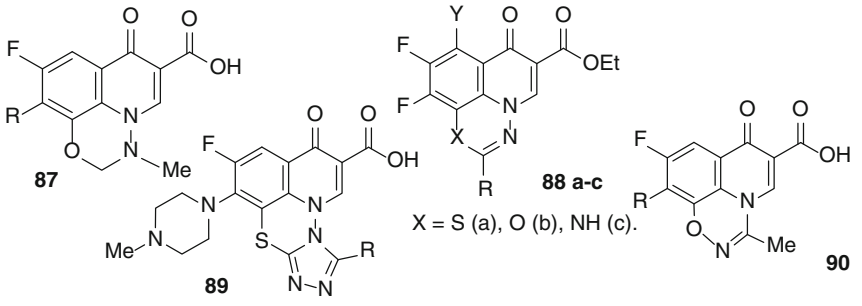
A number of ofloxacin analogues modified in position 10, including the well-known antibacterial drug pazufloxacin **84**, have been synthesized [263–265]. Some compounds of this series show a high activity towards a number of microorganisms, such as *Shigella flexneri*, *Proteus vulgaris* [263]. It is worth noting that (3S)-10-[*Cis*-(*3S,4S*)-3-amino-4-(fluoromethyl)pyrrolidin-1-yl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-*d,e*]

[1,4]benzoxazin-6-carboxylic acid **85** is more active than levofloxacin against *Staphylococcus aureus 870307* [266]. An analogue of ofloxacin, containing a macrocyclic fragment in position 6 has been described [267]. All kinds of modifications of the structure of ofloxacin have been performed by varying substituents not only in positions 6 and 10, but also in the oxazine ring. In particular, compounds **86** show a comparable with ofloxacin activity against Gram-positive and negative microorganisms, and a high activity towards methicillin-resistant strain of *S. aureus MR5867* [MIC 0,016–0,25 μg/ml for compound **86** (X = O, R = 3-cyclopropylaminomethyl-1-pyrrolidine)] (Scheme 39) [268].



Scheme 39 Structure of fluoroquinolones **84–86**

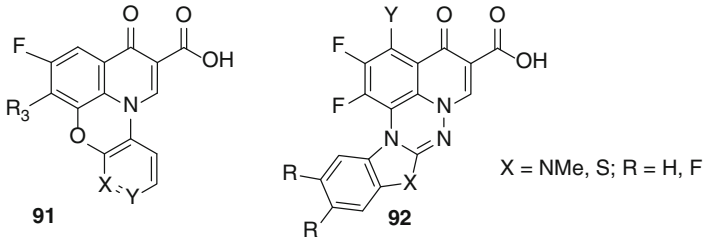
Marbofloxacin 87 is a representative of another promising group of tricyclic fluoroquinolones, pyridino[3,2,1-*i,j*]-1,3,4-benzoxadiazines, is widely used in veterinary practice (Scheme 40) [269].



Scheme 40 Structure of fluoroquinolones **87–90**

Synthetic methods to obtain other members of the family of [*i,j*]-annelated fluoroquinolones have been developed. For instance, derivatives of 1,3,4-thiadiazino[6,5,4-i,*j*]-, 1,3,4-oxadiazino[6,5,4-*i,j*]- and 1,2,4-triazino[5,6,1-*i,j*]-annelated quinolones **88a-c** have been obtained by means of cyclization of 2-polyfluorobenzoyl acrylates bearing hydrazide, thiosemicarbazide or amidrazone moieties in position 3 [270–275]. Thiadiazino-fused quinolones **88a** and compounds derived from displacement of fluorine atoms in positions 8 and 10 with cycloalkylimines are of great interest as promising compounds exhibiting not only

antibacterial but also other types of biological activity [276, 277]. Synthesis of tetracyclic quinolones **89**, in which the thiadiazine fragment is fused with both the pyridine and triazole rings has been described [278]. Activity of compounds **89** with R = H, Me against Gram-positive and Gram-negative bacteria is comparable with that of ofloxacin. Another core structure close to ofloxacin is 1,2,4-oxadiazino[*i,j*]-annelated fluoroquinolone **90** which was obtained by cyclization of 3-[1-(hydroxyiminoethyl)amino] acrylate [279]. The synthesis of tetracyclic fluoroquinolones **91** has been reported [280, 281]. The structure of novel pentacyclic fluoroquinolones **92** (Scheme 41), obtained by cyclization of ethyl 3-(benzazol-2-yl)hydrazino-2-polyfluorobenzoyl acrylates, was elucidated by X-ray crystallography [282–284].

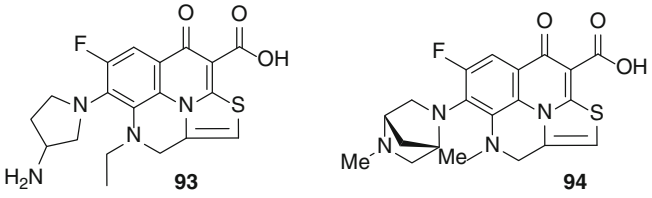


Scheme 41 Structure of fluoroquinolones **91, 92**

As a rule, cyclizations of 1-substituted 8-fluoroquinolones have an advantage in comparison with annelation of the pyridine ring to a benzazine moiety, thus allowing one to vary annelated fragments to a greater extent. However, the synthesis of levofloxacin is an exception, since the scheme suggesting to obtain first the optically active benzoxazine, as the key intermediate, followed by annelation of the pyridone fragment proved to be a more successful one.

2.2.7 Tetracyclic [*a,i,j*]-Annelated Fluoroquinolones

Several examples of tetracyclic [*a,i,j*]-annelated fluoroquinolones are available in the literature. In particular, compounds **93** and **94**, bearing 3-aminopyrrolidine and (*1S,4S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptane fragments, respectively are considered to be rather promising because they both exceed ofloxacin in antibacterial activity (Scheme 42) [285, 286].



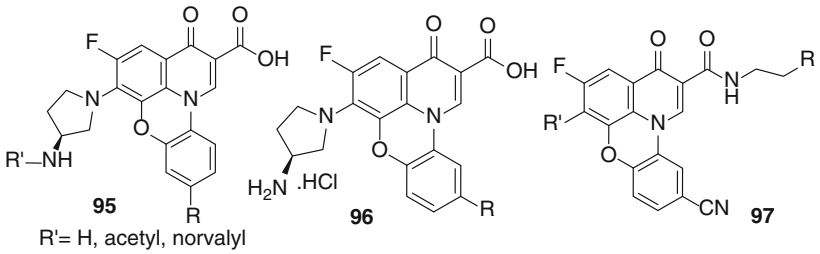
Scheme 42 Structure of tetracyclic fluoroquinolones **93**, **94**

3 Other Types of Biological Activity of Fluoroquinolones

During the last decades compounds of the fluoroquinolone family proved to be not only effective inhibitors of bacterial enzymes; their antineoplastic [287], antiviral [41] (including concerning HIV [288]), anti-diabetic [289] and other types [290, 291] of biological activity have been intensively elucidated.

3.1 Anticancer Activity

Some representatives of the fluoroquinolone family, especially polycyclic compounds, are capable of inhibiting topoisomerase II, the key enzyme for replication DNA, and this is why they are promising for development of antineoplastic drugs [172, 292, 293]. In particular, a profound antineoplastic activity is demonstrated by quinobenzoxazines **95–97** (Scheme 43) [293–298]. Fluoroquinolone **95** (R'=H) is more active towards some tumor cells than such antineoplastic drugs, as adriamicin, camptotecin and etoposide [299]. Relationships between the nature of substituents in the amino fragment and the benzene ring of compounds **95–96** and their abilities to suppress the growth of tumor cells have been studied. Compounds with R'=H and R=Cl, NO_2 were shown to inhibit not only topoisomerase II, but also topoisomerase I [280, 299–301]. Amides **97** proved to suppress effectively the growth of HCT-116 cells, IC_{50} values 0,03–0,4 μM [295].

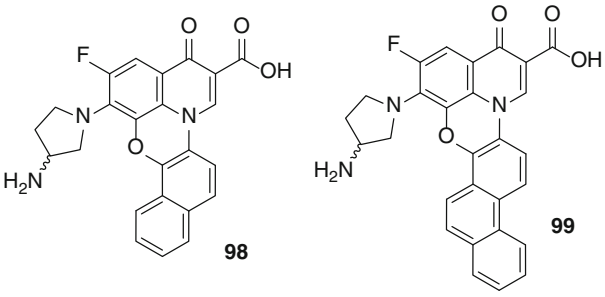


Scheme 43 Structure of fluoroquinolones **95–97**

Further steps to modify the structure quinobenzoxazines **95** involve annelation of the benzene rings to the benzoxazine fragment, as illustrated by the synthesis of benzo- and dibenzoderivatives **98** and **99** (Scheme 44) [299, 302]. Research studies on activity of pentacyclic derivatives **98** towards a number of tumor cells have shown that *R*-isomers are much more active, than *S*-isomers (Table 7). Also it has been revealed that a molecular target for fused fluoroquinolones **99** is the site of DNA capable of forming the quadruplex [303]. It has been shown that R-isomer **99** is characterized by a strong linkage with G-quadruplex and a low influence on topoisomerase II, while the *S*-isomer **99** has a strong linkage with topoizomerase II and a low interaction with G-quadruplex [296].

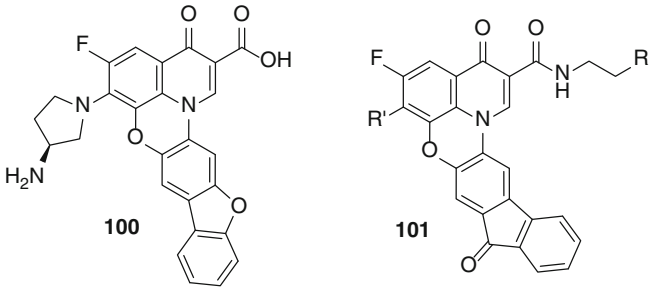
Table 7 Inhibition of cancer cells by pentacyclic fluoroquinolones **98**

Cell lines	Value IC_{50} *in vitro*, μM	
	(*S*)-isomer	(*R*)-isomer
B16 (melanoma)	0.2	0.02
MDA-231 (breast cancer)	0.08	0.005
H226 (lung cancer)	0.03	0.01
HT-29 (colon cancer)	0.05	0.03
DU 145 (prostate cancer)	0.06	0.03



Scheme 44 Structure of fluoroquinolones **98**, **99**

The data of biological tests on activity of compound **100** (drug QQ58), as an intercalator of DNA [304] confirmed that this compound inhibits human telomerase (IC_{50} 28 μM); in organisms it is transformed into qarfloxacin which is linked with DNA G-quadruplexes [300, 304–306]. Polynuclear fluoroquinolones, containing the amide fragment, for example **101** (Scheme 45), have been shown to inhibit effectively the HeLa (mammalian cancer) growth (IC_{50} 0,1–0,2 μM) [303, 307, 308].



Scheme 45 Structure of fluoroquinolones **100**, **101**

Other fused fluoroquinolones, derivatives of benzazolotriazino[*i,j*]-annelated quinolon-6-carboxylic acids **92** have shown anticancer activity [309]. Biological tests on 9 types of tumors revealed that annelation of 1-methylbenzimidazo fragment to the triazine ring is more effective for suppression of cell growth, than that of the benzothiazole ring. An increase in numbers of fluorine atoms in the benzene rings of quinoline or benzazole fragments enhance antineoplastic action of pentacyclic

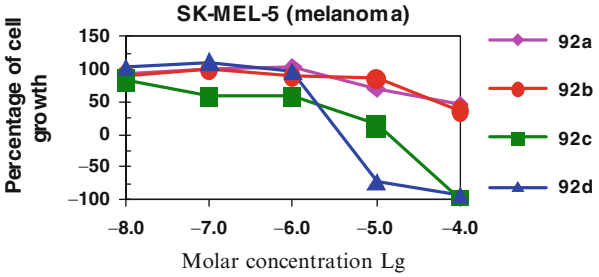
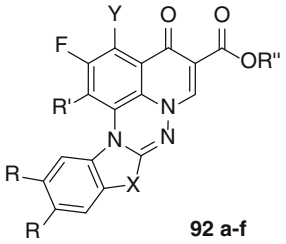


Fig. 2 Cells growth suppression for derivatives **92a-d**



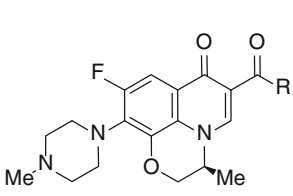
92 a-f

92: X=S, Y=R=R'=R''=H (a),
X=NMe, Y=R=R'=H, R''=Et (b),
X=NMe, Y=R=R'=R''=H (c),
X=NMe, Y=R=R'=F, R''=H (d),
X=NMe, Y=R=F, R''=H,
R'=pyrrolidin-1-yl (f).

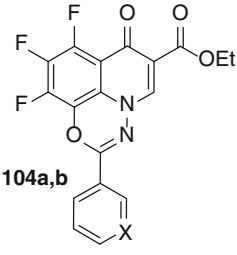
Scheme 46 Structure of fused fluoroquinolones **92**

derivatives; acids suppress growth of cells more strongly, than the corresponding ethyl esters. The biggest effect on melanoma has been observed *in vivo* experiments for fluoroquinolone **92d** (Scheme 46, Fig. 2) [310].

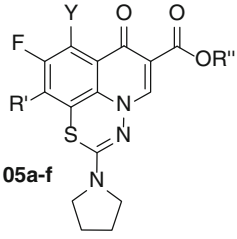
Derivatives of levofloxacin **103** (Scheme 47), bearing in position 3 a lipophilic fragment, or the benzothiazole fragment instead of the carboxyl group, proved to exhibit antineoplastic activity (Table 8) [311]. The highest level of activity against glioblastoma has been observed for the ester **103a**.



103



104a,b



105a-f

103: R = $OCH_2OC(O)C_{11}H_{23}$(a), $OCH_2OC(O)C_{17}H_{35}$(b), NHC_8H_{17}(c);

104: X = C-NO_2(a), N (b); 105: R''=Et, Y=R'=F (a), Y=R'=$Me_2N(CH_2)_3NH$ (b),
Y = H, R'=F (c); R''=H, Y=H, R'=F (d), Y = R' = F (f).

Scheme 47 Structure of fluoroquinolones **103–105**

Table 8 Activity of levofloxacin derivatives **103** against some cancer cells

Compound	IC_{50} *in vitro,* mkM				
	U373-MG (glioblastoma)	A549 (lung cancer)	PC-3 (prostate cancer)	LoVo (colon cancer)	MCF-7 (breast cancer)
Levofloxacin	188	70	238	67	622
103a	0.2	65	86	0.3	0.3
103b	0.9	593	100	4	12
103c	2.3	2.2	1.5	0.8	2.1

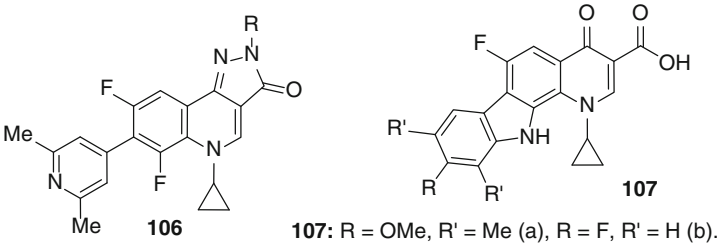
Table 9 Inhibitory and cytotoxicity properties of pyrazoloquinolones **106**

R	HeLa cell topo II inhibitory properties (EC_{50}, μM)	Cytotoxicity properties for P388 *in vitro* (IC_{50}, μM)
$(CH_2)_2NMe_2$	2.6	0.26
$(CH_2)_3NMe_2$	1.7	0.16
Cyclohexyl	0.9	0.68
$CH(CH_2CH_2)_2O$	1.7	0.29
$CH(CH_2CH_2)_2NMe$	3.2	0.094
$CH(CH_2CH_2)_2CHNH_2$(*cis*)	0.5	0.44
$CH(CH_2CH_2)_2CHNMe_2$(*cis*)	1.7	0.067
$CH(CH_2CH_2)_2CHNMe_2$(*trans*)	4.4	0.26
1-Cyclopropyl-6,8-difluoro-7-(2,6-di-methyl-4-pyridinyl)-4*H*-4-oxoquinoline-3-carboxylic acid	7.6	29
1-Cyclopropyl-6,8-difluoro-7-(2,6-di-methyl-4-pyridinyl)-4*H*-quinoline-4-one	17	15

Antineoplastic activity of fluorine-containing derivatives of 1,3,4-oxa(thia)-diazine[6,5,4-*i,j*]quinolon-6-carboxylic acids **104, 105** has been studied on cultures of 60 lines of cancer cells for nine groups, such as leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, mammalian cancer [309, 310]. In the series of thiadiazinoquinolines the highest effect on antineoplastic activity gas been observed for compounds **105a** and **105b** bearing such pharmacophoric fragment, as N,N-dimethyl-1,3-diaminopropane. In case of compound **105b** the full death of nearly all tumor cells MCF7 and SF-268 (more than 90 %) has been reached. Biological tests of compounds **105a,c,d,f** have shown that the presence of a fluorine atom in position 8 facilitates suppression of cell growth. Also a high activity of compound **105a** towards leukemia has been established [309, 310].

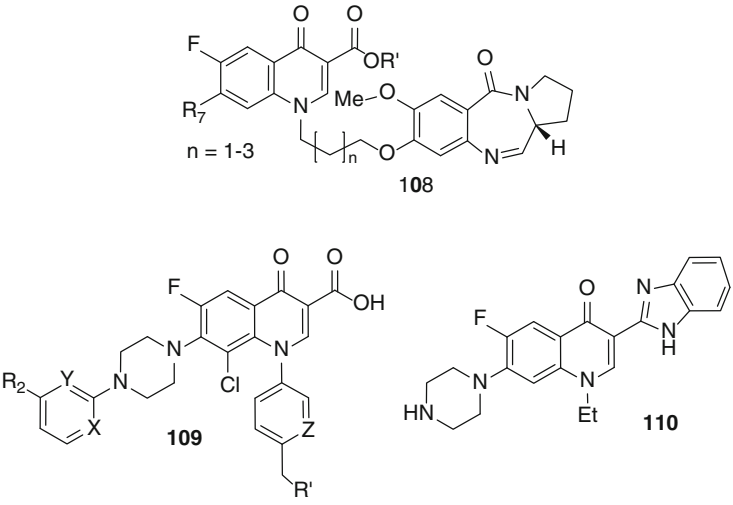
Not only [*i,j*]-annelated fluoroquinolones, but also polycyclic fluoroquinolones, in which an additional ring is annelated to [*c*]- or [*h*]-sides proved to possess antineoplastic action. Research studies on antineoplastic activity of 5-cyclopropyl-6,8-difluoro-7-(2,6-dimethyl-4-pyridinyl)-5H-pyrazolo[4,3-*c*] quinolin-3(2H)-ones **106** have shown that derivatives containing the cyclohexyl group in position 2 are the most effective inhibitors of topoisomerase II of HeLa cells (mammalian cancer), while the dimethylaminocyclohexyl compound has shown the best data on cytotoxicity towards P388 (leukemia) cells (Table 9) [312].

6-Fluoro-4-oxopyridino[2,3-*a*]-carbazol-3-carboxylic acids **107** inhibit MCF-7 (breast cancer) and A549 (lung cancer), activity of **107b** towards MCF-7 is twice higher, than that of ellipticine (Scheme 48) [198].



Scheme 48 Structure of fluoroquinolones **106**, **107**

Also a number of bicyclic fluoroquinolones are capable of suppressing the growth of tumor cells. Incorporation of pyrrolo[2,1-*c*][1,4]benzodiazepine fragment in position 1 of fluoroquinolones resulted in compounds **108**, which inhibit the growth of HT-29 (colon cancer) cells and A549 (lung cancer) up to 80 % [313]. Derivatives of 1-phenylsubstituted fluoroquinolones **109** suppress the growth of Solo205 (carcinoma) cells (IC_{50} values 2–20 nM) [314]. 3-Benzimidazolyl fluoroquinolone **110** and its analogues (Scheme 49), including [*i*,*j*]-oxazino



Scheme 49 Structure of fluoroquinolones **108–110**

Table 10 Tuberculostatic activity of some fluoroquinolones

Quinolone	MIC, μg/ml	Quinolone	MIC, μg/ml
Sparfloxacin	0.25	Trovafloxacin	16
Sitafloxacin	0.25	Grepafloxacin	1
Clinafloxacin	0.5	Pefloxacin	8
Gatifloxacin	0.12	Tosufloxacin	16
Ciprofloxacin	0.5	Temafloxacin	4
Moxifloxacin	0.5	Fleroxacin	6.25
Levofloxacin	0.5	Enoxacin	8
Ofloxacin	1	Oxolinic acid	32
Gemifloxacin	4	Flumequin	64
Garenofloxacin	2	Pipemidic acid	128
Norfloxacin	4	Nalidixic acid	128

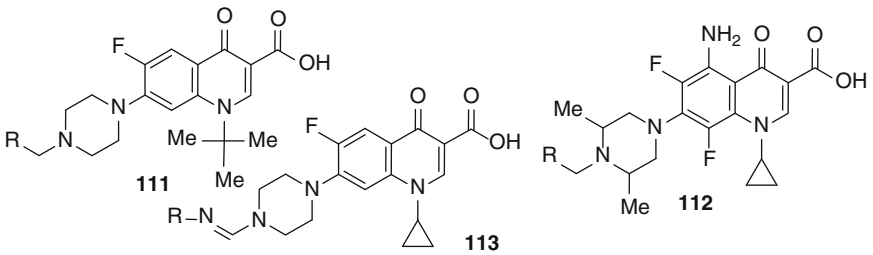
annelated compounds, proved to suppress the growth of tumor KV, A2780 and Bel7404 cells [315].

Rather high antineoplastic activity of ciprofloxacin derivatives, containing a substituent in position 4 of the piperazine fragment has been shown [302]. Elucidation of the "structure-activity" relationships for 1-(2-thiazolyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acids has shown that several compounds of this series exhibit activity, comparable with the well-known drug *etoposide* [316–318]. Also the data on activity of amides of 7-substituted 1-(2-thiazolyl)- and 1-(2-benzothiazolyl)-1,8-naphthyridin-4-on-3-carboxylic acids have been reported [319]. Ethyl 1-(4-cyano-2,3,5,6-tetrafluorophenyl)-6,7,8-trifluoro-4-oxo-1,4-dihydroquinolin-3-carboxylate proved to inhibit the phosphorylation process of transcription STAT3 activator that plays an important role for cancer therapy [320].

3.2 Tuberculostatic Activity

Being effective inhibitors of DNA-gyrase of mycobacteria some derivatives of fluoroquinolones are important for therapy of rifampicin-resistant tuberculosis [321]. In particular, values of minimum inhibitory concentrations against *M. tuberculosis* for a number of elucidated fluoroquinolones proved to be in the range from 0,12 to 128 μg/ml (Table 10) [322, 323].

An important synthetic approach for development of fluoroquinolones which are active against *Mycobacterium tuberculosis* appears to be introduction of isoniazide and pyrazinamide residues into the piperazine fragment in position 7. Indeed, 1-*tert*-butyl substituted fluoroquinolones **111** and 1-cyclopropyl-5-amino-fluoroquinolones **112** proved to exhibit a high activity towards *Mycobacterium tuberculosis in vivo* [38]. The minimum inhibitory concentration against *M. tuberculosis* $H_{37}R_v$ for compound **113b** is 0,78 μg/ml (Scheme 50) [324]. Also quinolones, bearing residues of hydrazides of substituted benzoic acids, which can be regarded as

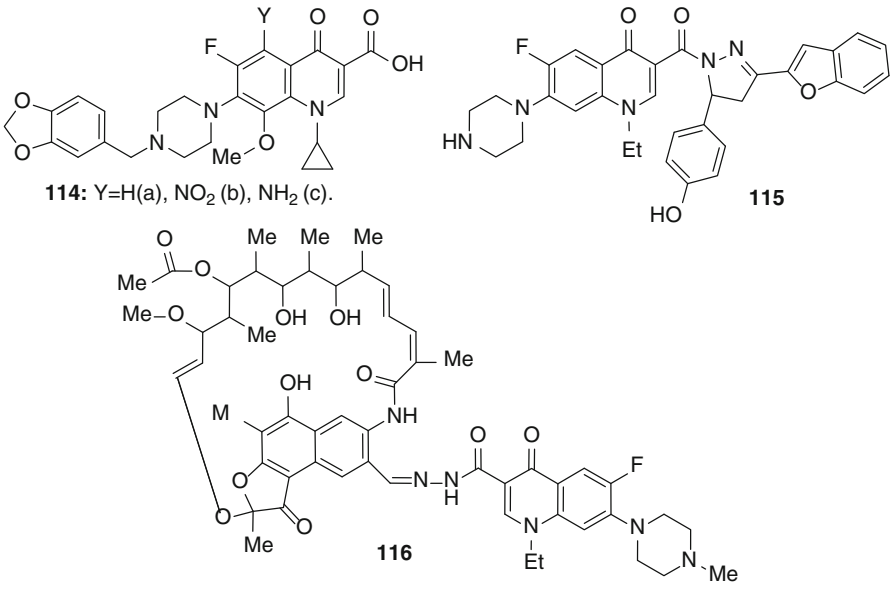


111, 112: R=(pyridin-4-yl)-C(O)NHN=C(Me)(a), (pyrazin-2-yl)-C(O)NHCH$_2$(b).
113: R=(pyridin-4-yl)-C(O)NH(a), (pyrazin-2-yl)-C(O)(b).

Scheme 50 Structure of fluoroquinolones **111**–**113**

isosters of isoniazide, proved to be active compounds (MIC 0,5 μg/ml for multiresistant *M. tuberculosis A8 241*) [325].

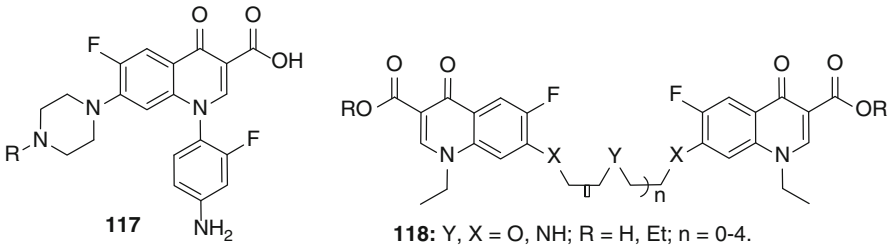
1-Cyclopropyl-8-methoxyquinolones **114** are active against *Mycobacterium tuberculosis,* its multi-resistant strains, as well as *Mycobacterium smegmatis* [326]. Derivative **115** possesses tuberculostatic activity against *Meningitis tuberculosis* $H_{37}R_v$ (MIC 0,16–0,35 μg/ml) [327]. 1-[(6′-Fluoro-1′,4′-dihydro-7-(4”-methyl-1”-piperazinyl)-1′-ethyl-4′-oxo-3′-quinolylamido)-3-iminomethyl]-rifampicin **116** proved to exhibit a considerable tuberculostatic activity (Scheme 51) [328].



114: Y=H(a), NO_2 (b), NH_2 (c).

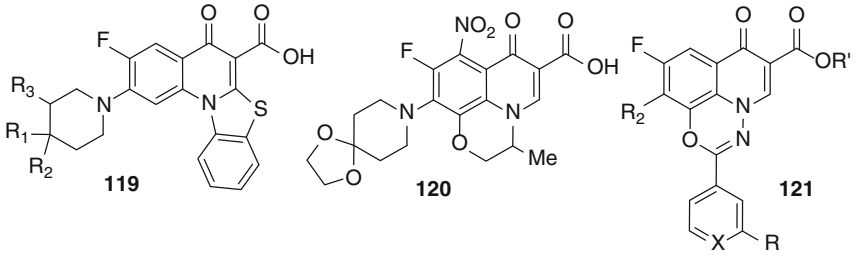
Scheme 51 Structure of fluoroquinolones **114**–**116**

1-(4′-Amino-2′-fluoro)phenyl substituted fluoroquinolones **117** (R = H, Me) inhibit the growth of *M. tuberculosis* [329]. Incorporation of aminoester or polyethyleneamino fragments has been suggested to increase their ability to penetrate through cellular membranes. Indeed, fluoroquinolones **118** have been established to possess a high specific activity against mycobacteria and a low toxicity [330]. Tuberculostatic activity of derivatives **118** (R = H; X, Y = 0; n = 4) proved to be five times higher than that of pefloxacin (Scheme 52).



Scheme 52 Structure of compounds **117**, **118**

Several compounds [331] of the benzothiazolo[3,2-*a*]quinolone-6-carboxylic acids **119** family (Scheme 53) exhibit high tuberculostatic activity relative to multiresistant strain of *M. tuberculosis* (Table 11).



Scheme 53 Structure of fluoroquinolones **119–121**

Ofloxacin and its analogs are promising drugs for tuberculosis treatment. Ofloxacin (daily dose 300–800 mg) and levofloxacin (250–500 mg a day) in

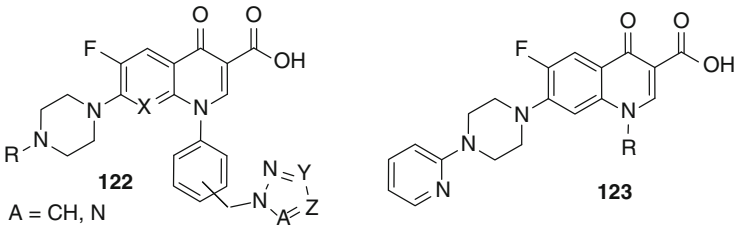
Table 11 Tuberculostatic activity of fluoroquinolones **119**

	MIC, μg/ml		
R^1, R^2, R^3	*Mycobacterium tuberculosis*	Multiresistant strain of *M. tuberculosis*	*M. smegmatis* ATCC 14468
R^1 = pyperidin-1-yl, $R^2 = R^3 = H$	0.39	0.19	6.53
R^1 = 4-ClC_6H_4, R^2 = OH, R^3 = H	0.36	0.36	2.98
$R^1 = R^2$ = H, $R^3 = Et_2NC(O)$	0.18	0.08	3.15
R^3 = H, R^1, $R^2 = OCH_2CH_2O$	0.86	0.86	6.89

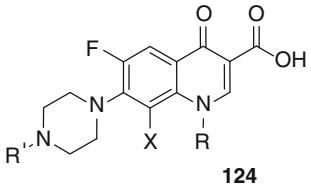
combination with *p*-aminosalicylic acid, cycloserine, or ethionamid are effective for the treatment of multi-resistant strains of tuberculosis. On using of these fluoroquinolones, a relatively high concentration in cells is reached, that increasing their antibacterial activity [38]. Derivatives of ofloxacin, containing the nitro group in position 8, e.g. **120** proved to possess a high tuberculostatic activity [332]. Also compounds showing tuberculostatic activity have been found among oxadiazinoquinolines **121** and thiadiazinoquinolines **105** (MIC 0,2–0,4 μg/ml) [276, 277].

3.3 Antiviral Activity

Fluoroquinolones **122**, bearing the (triazolylmethyl)phenyl fragment in position 1 and an aryl substituent in position 4 of piperazine, are capable of protecting the HIV-infected cells from a virus-induced destruction (IC_{50} 0,25–0,7 μM). They appear to be a new structural type of effective drugs for treatment and prevention of viral diseases caused by HIV retroviruses [333]. Fluoroquinolones **123** with 4-(2′-pyridinyl)-1-piperazine fragment in position 7, inhibit reverse transcriptase of HIV-1 [334]. 8-Difluoromethoxy- and 8-trifluoromethylcarboxylic acids **124** inhibit replication of HIV-1, while CF_3- derivatives are more active against HIV-1 than the corresponding difluoromethoxy compounds (Scheme 54, Table 12) [335–338].



123, 124: R=t-Bu (a), cyclopropyl (b), Me (c). X=$OCHF_2$, CF_3.



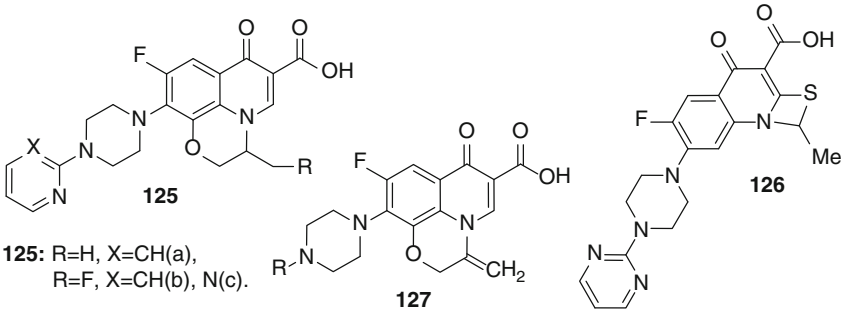
Scheme 54 Structure of fluoroquinolones **122–124**

[*i,j*]-Annelation of the oxazine ring is favorable for exhibiting of antiviral activity, but does not lead to such promising compounds, as 8-methoxy- and

Table 12 Inhibition of HIV-1 by **124**

R	R'	IC_{50}, μM	
		8-CF_3	8-$OCHF_2$
Me	2-$OMeC_6H_4$	0.054	0.35
Et	2-$OMeC_6H_4$	0.11	0.22
Cyclopropyl	2-$OMeC_6H_4$	0.069	0.56
Me	2-pyrimidinyl	0.049	0.31
Et	2- pyrimidinyl	0.095	0.47
Cyclopropyl	2- pyrimidinyl	0.19	3.7
Me	2-pyridyl	0.014	0.24
Et	2- pyridyl	0.026	0.89
Cyclopropyl	2- pyridyl	0.065	0.49

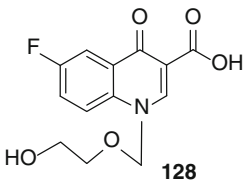
difluoro-methoxy derivatives [339]. Fluoroquinolone **125c** is more active against the virus HIV-1, than thiazeto derivative **126** [336]. Values IC_{50} 3,7 μM for **125a** and 1,7 μM for **125b** have been found, while values EC_{50} 0,074 μg/ml for **125c** and 0,4 μg/ml for **126** have been obtained. Also a number of tricyclic fluoroquinolones **127** proved to possess a high activity (EC_{50} 0,008–2.3 μg/ml) (Scheme 55) [340]. Also effective compounds against HIV-1 have been discovered in the series of the Mannich bases of norfloxacin [341].



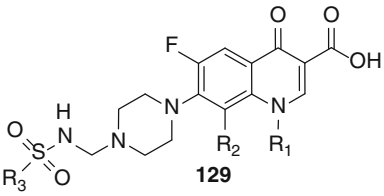
Scheme 55 Structure of fluoroquinolones **125**–**127**

Fluoroquinolone **128** bearing the (2-hydroxyethoxy)methyl fragment at N-1 is active against **herpes virus** HSV-1 (EC_{50} 2,30 μM), however the level of its activity is lower than that of *acyclovir* (EC_{50} 1,09 μM) [41]. 8-Trifluoromethylquinolones **124** have been reported to suppress **human cytomegalovirus** [342]. Fluoroquinolones **129**, containing the sulphamidomethyl group in a piperazine fragment, are active against **influenza** H1N1, H3N2 and H5N1 **viruses** [343]. Tricyclic fluoroquinolones **130, 131** were found to possess a high activity against hepatitus B virus (IC_{50} 0,1 μM) (Scheme 56) [344, 345].

Ciprofloxacin and levofloxacin are recommended for treatment of patients after transplantation surgery operations in order to prevent the disease caused by poliomavirus BK [346].

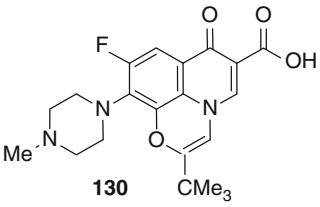


128

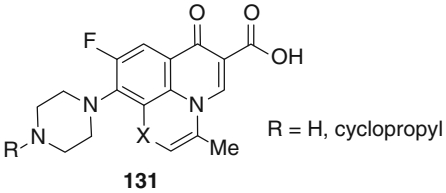


129

129 :R_1=Et, cyclopropyl; R_2=H,OMe;
R_3=2-pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl.



130

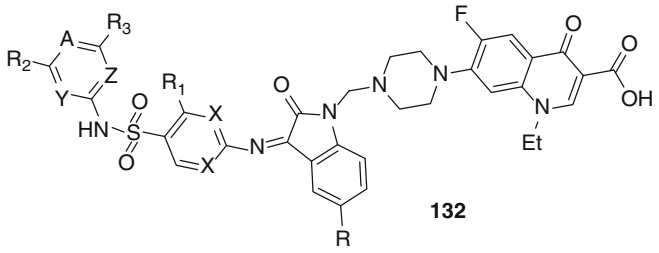


131

Scheme 56 Structure of fluoroquinolones **128**–**131**

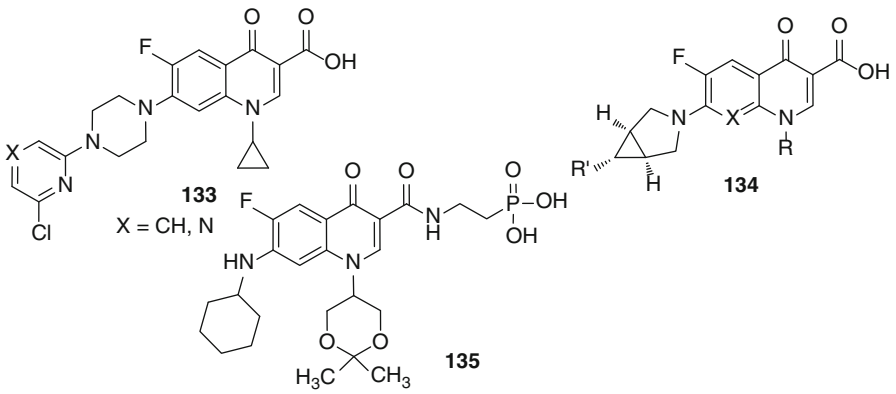
3.4 Other Types of Biological Activity

Some fluoroquinolones appear to be active against **fungi and parasites**. For instance, the Mannich derivatives of *norfloxacin* **132** demonstrate a considerable antifungal activity against *Histoplasma capsulatum.* One of compounds of this family is more active than *clotrimazole* towards *Microsporum audouinii*, while other derivatives surpass *clotrimazole* in relation to *Cryptococcus neoformans* or *Microsporum gypsum*. From all derivatives **132** which have been studied (Scheme 57), compound with R=Br, X=N, $R^1=NH_2$, Y-Z=CH, A=COMe, R^2-R3=OMe proved to exhibit the highest antifungal activity (MIC for *Cryptococcus neoformans* and *Microsporum audouinii* 0,6 μg/ml) [341].



Scheme 57 Structure of fluoroquinolones **132**

Moxifloxacin, gatifloxacin, trovafloxacin, and grepafloxacin belong to a new generation of fluoroquinlones, showing anti-parasitic activity against *Toxoplasma gondii* and *Plasmodium falciparum* which cause such severe diseases as toxoplasmosis and malaria, respectively. These fluoroquinolones are targeting at the DNA-gyrase, located in a top layer of parasites [347]. For example, the IC_{50} value for trovafloxacin against *Toxoplasma gondii* is 0,96 μM. The data on activity of fluoroquinolones **133** against parasites (*Coccidia*) [348], and activity of 7-(3′-azabicyclo[3.1.0]hexyl)quinolones **134** in relation to plasmodium have recently been reported (Scheme 58) [149].

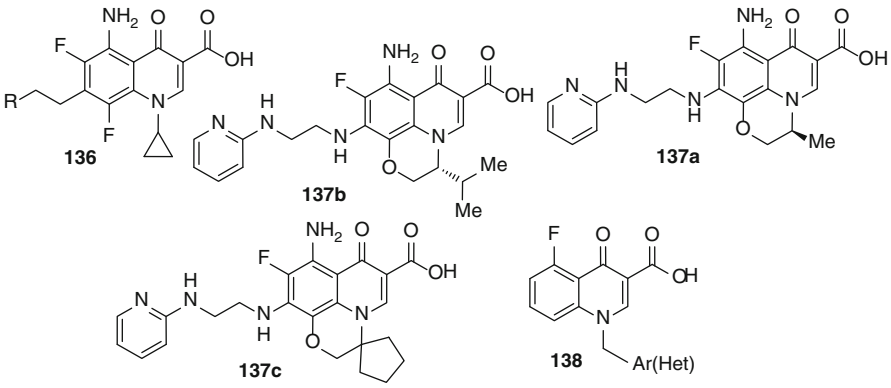


Scheme 58 Structure of fluoroquinolones **133–135**

Table 13 Inhibition of GSK by fluoroquinolones **136, 137**

Compound	R	IC_{50}, nM
136a	4-$NH_2C_6H_4$	900
136b	C_6H_5	440
136c	imidazol-1-yl	3,400
136d	$CH_2C_6H_5$	45
136e	(imidazol-1-yl)methyl	45
136f	$CH_2CH_2C_6H_5$	290
136g	(pyridin-2-yl)amino	22
137a		44
137b		31
137c		12

Some fluoroquinolones have been shown to exhibit **cardiovascular, hypertensive**, and **antitrombocyte** activities. For instance, compound **135** inhibits aggregation of trombocytes [349]. According to the recently published data, 5-amonofluoroquinolones **136** and **137** are active as **glicogensyntase-kinase-3β inhibitors** (GSK, serine-treonine-proteinkinase) [265]. Bi- and tricyclic fluoroquinolones, bearing the fragment of N-(2-pyridinyl)ethylenediamine appear to be promising GSK inhibitors (Table 13) [265]. **138**, their 8-fluoro- and 5,8-difluoroderivatives proved to be selective allosteric **modulators of M1 receptor**, activation of which is important for therapy of the Alzheimer's disease (Scheme 59) [350–353].



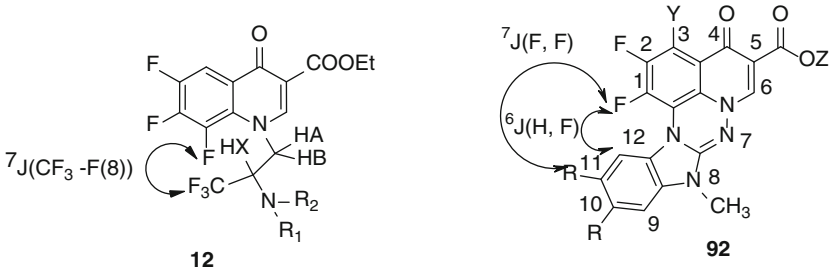
138: Het = 1-methyl-2,3-dihydroindol-5-yl, 1-methylindazol-5-yl, indazol-5-yl, 5-arylpyridin-2-yl.

Scheme 59 Structure of fluoroquinolones **136–138**

4 Structure and Spectral Characteristics

The structure of fluoroquinolones has been elucidated in crystals and solutions. The data on X-ray crystallography analysis of fluoroquinolines are available in the literature for both quinolones [89, 123, 354, 355], and their polycyclic [204, 231, 232, 270, 271, 282, 283, 356] condensed systems.

The ^{1}H, ^{13}C and ^{19}F NMR spectra for the series of fluoroquinolines have been registered and analyzed. ^{1}H, ^{13}C NMR spectra of fluoroquinolones bearing rather complicated optically active fragments, including heteronuclear correlation experiments, have been discussed in the literature [164–168]. Elucidation of NMR ^{19}F spectra of compounds **12** has revealed long-range coupling constants $^{7}J_{F\text{-}F}$ between the trifluoromethyl group and fluorine atom in position 8, which are realized through space due to vicinity of interacting spins [39]. The ^{19}F NMR spectra of benzimidazo [2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinoline ring system **92** demonstrate unusual through space ^{1}H-^{19}F and ^{19}F-^{19}F spin-spin interactions with coupling constants $^{7}J(F^{1}, F^{11}) = 3.5–4.0$ Hz and $^{6}J(F^{1}, H^{12}) = 2.0–3.0$ Hz (Scheme 60) [284].



Scheme 60 Long-range coupling constants in compounds **12**, **92**

5 Complexes of Fluoroquinolones with Metals

Due to the presence of the carboxyl and β – oxo groups, as well as azaheterocyclic fragments, fluoroquinolones have a profound ability to form metal-chelates, and other ionic structures. It is known that complexes with metals may enhance activity of fluoroquinolones due to a better solubility and endocellular accumulation [357, 358]. The crystal structures of a number of metal complexes, results of their thermal analysis, IR and NMR spectra of complexes and their bioactivity have been considered [359]. In the recently published review article [360] the data concerning the structure and properties of metal complexes of fluoroquinolones, and their interaction

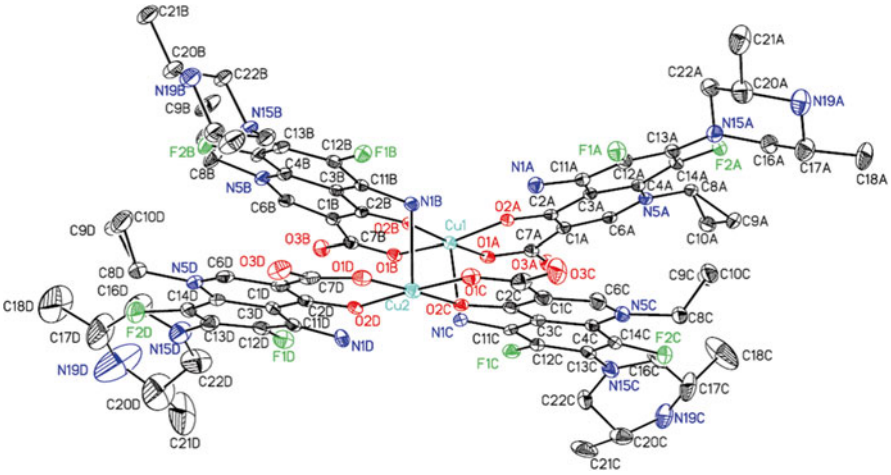
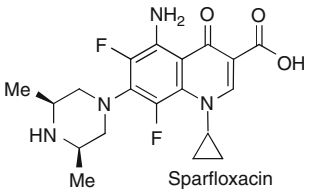


Fig. 3 Structure of complex $Cu_2(sflx)_2$ (Reproduced with permission of Elsevier [365])

with DNA have been analyzed. Also physical and chemical characteristics, as well as pharmacokinetic data and antibacterial properties of fluoroquinolones complexes with a variety of metals have been reviewed [361].

The Cu(II)-complex of ciprofloxacin was shown to possess a high activity against *Mycobacterium tuberculosis* than the parent compound [362]. An enhanced solubility of metal complexes in lipids facilitates their transport into bacteria cells, while an easily proceeding reduction of metal leads to the formation of Cu(I) and activation of oxygen which kills mycobacteria. Authors came to a conclusion that redox-active metal complexes are very promising compounds for development of highly active antitubercular drugs. Indeed, the minimum inhibitory concentration for enrofloxacin complex $Cu(erx)_2(H_2O)$ against *E. coli* и *P. aeruginosa* is 0.125 μg/ml, while the same index for the parent enrofloxacin is 1.0 μg/ml [363]. Antibacterial activity of N-propyl norfloxacin (pr-norf) complex with $CuCl_2$ and phenanthroline (phen) [Cu(pr-norf)(phen)Cl] has been was reported [364]. For instance, the formation of sparfloxacin (sflx) (Scheme 61) dimeric complex with Cu(II) [$Cu_2(sflx)_2$] and mononuclear complex with phenanthroline [$Cu(phen)(sflx)H_2O$] has been shown (Figs. 3 and 4) [365].



Scheme 61 Structure of sparfloxacin (sflx)

Antiproliferative effect of sparfloxacin and its metal complexes against hormone independent BT20 breast cancer cell line has been studied (Fig. 5) [365].

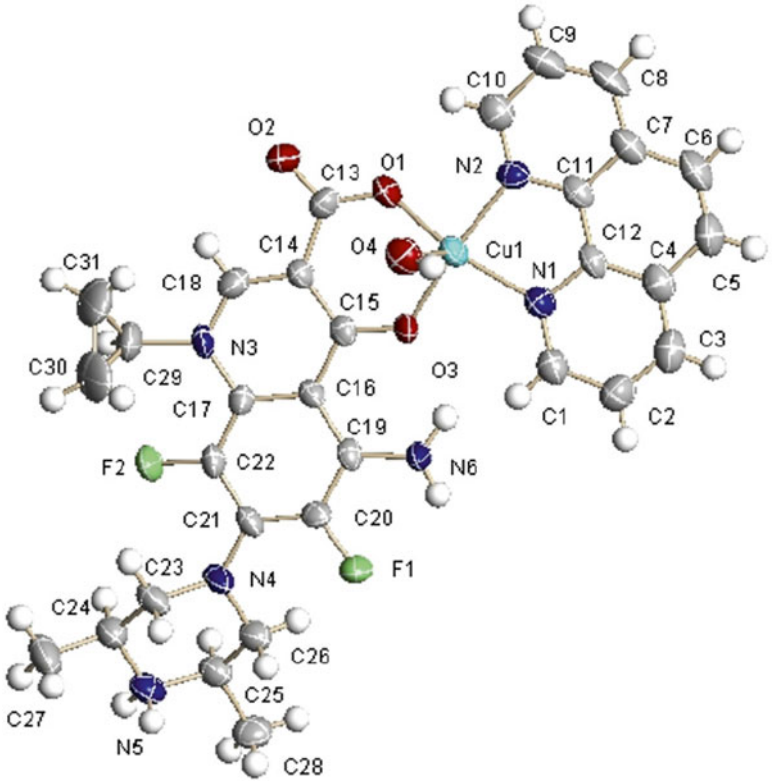


Fig. 4 Structure of complex Cu(phen)(sflx)H_2O (Reproduced with permission of Elsevier [365])

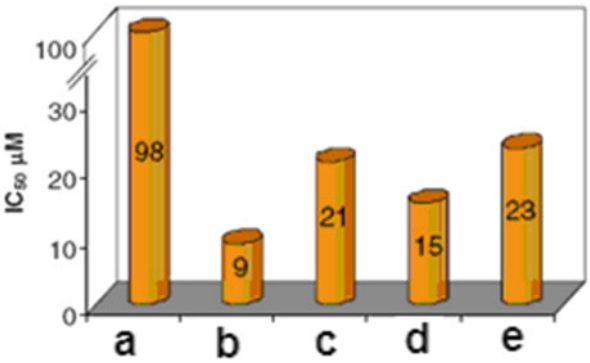


Fig. 5 Suppression of cells growth by sparfloxacin and its metal complexes, a- spfx, b-$Cu_2(sflx)_2$, c-[Cu(bpy)(sflx)H_2O], d-[Cu(phen)(sflx)H_2O], e-[Cu(df)(sflx)H_2O]; bpy = bipyridine, phen = phenanthroline, df = 4,5-diazafluoren-9-one (Reproduced with permission of Elsevier [365])

Coordination of sparfloxacin with copper in the form of dimeric complex $Cu_2(sflx)_2$ has been established to diminish the value of inhibitor concentration IC_{50} (μM) in approximately ten times. These data are in agreement with a hypothesis that biological activity of fluoroquinolones is in many respects caused by their ability for

metal chelate formation. Antitumor activity of moxifloxacin-copper complexes against breast cancer cell lines has also been described [366].

Complex of norfloxacin $[Fe(nf)_2(H_2O)_2]Cl_3 \cdot 6H_2O$ was shown to exhibit a higher antibacterial activity than the parent norfloxacin against *E. coli* and *Bacillus dysenteriae bacteria* [367]. Also it is worth noting that antimicrobial activity of cobalt complexes of ciprofloxacin is less, than that of copper complexes [368].

The reaction of ciprofloxacin (cfH) with metal salts in the presence of aromatic polycarboxylate ligands (or under basic conditions) has been found to give original metal–cfH complexes, for example, $[Ba_2(cf)_2(1,4\text{-bdc})(H_2O)_2]\cdot H_2O$ and [Mn(cfH)(1,3-bdc)] (bdc = benzenedicarboxylate). The structure of $[Ba_2(cf)_2(1,4\text{-bdc})(H_2O)_2]\cdot H_2O$ consists of unique two-dimensional arm-shaped layers (Fig. 6), while the second complex contains double-chain-like ribbons constructed from $[Mn_2(cfH)_2(CO_2)_2]$ dimers and 1,3-bdc (Fig. 7) [369].

Supramolecular structure of cadmium complexes of ciprofloxacin $[Cd_2(cf)_2(bptc)(H_2O)_2]\cdot 8H_2O$ is shown in Fig. 8 [369]. Two units are connected together by μ_3-O atoms of carboxylic groups from cf ligands in an edge-sharing mode to form $[M_2(cfH)_2(H_2O)_2]$ dimers.

Complexes of norfloxacin with zinc(II), such as $[Zn(nf)_2]\cdot 4H_2O$ and $[Zn(H_2O)_2(nf)_2](NO_3)_2$, were found to exhibit a strong blue fluorescent emission [370]. The complex of Zn(II) with enrofloxacin and pyridine, as the second N-donative ligand, $[Zn(erx)_2(py)_2]\cdot 6H_2O\cdot MeOH$ has been obtained (Fig. 9). Such complexes were found to interact with CT-DNA, thus demonstrating their ability to bind with DNA. According to the data obtained by using the UV spectroscopic titration technique, the binding strength for $Zn(orx)_2(py)_2$ corresponds to the highest K_b value [371].

The formation of ofloxacin complexes with magnesium has been studied by using NMR ^{1}H and 2D ^{1}H-^{13}C HSQC methods [372]. Behavior of coordinative compounds of ciprofloxacin, levofloxacin and lomefloxacin with Al(III) in water solutions has been elucidated by NMR ^{1}H and ^{13}C spectroscopy [373]. Tetrakis[4-(3-carboxy-1-ethyl-6-fluoro-4-hydroxonio-1,4-dihydro-7-quinolyl)-1-methyl-piperazin-1-ium] di-μ_2-chlorido-bis[tetrachloridobismuthate(III)] tetrachloride octahydrate, $(C_{17}H_{22}FN_3O_3)_4[Bi_2Cl_{10}]Cl_4\cdot 8H_2O$, is composed of edge-shared centrosymmetric dinuclear $[Bi_2Cl_{10}]^{4-}$anions, Cl^-anions, dihydrogen pefloxacinium cations and water molecules. The Bi^{III} coordination polyhedron is a distorted octahedron [374].

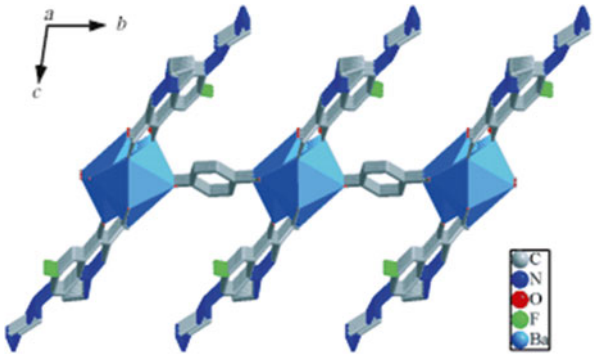


Fig. 6 Structure of complex $[Ba_2(cf)_2(1,4\text{-bdc})(H_2O)_2]\cdot H_2O$ (Reproduced with permission of Wiley [369])

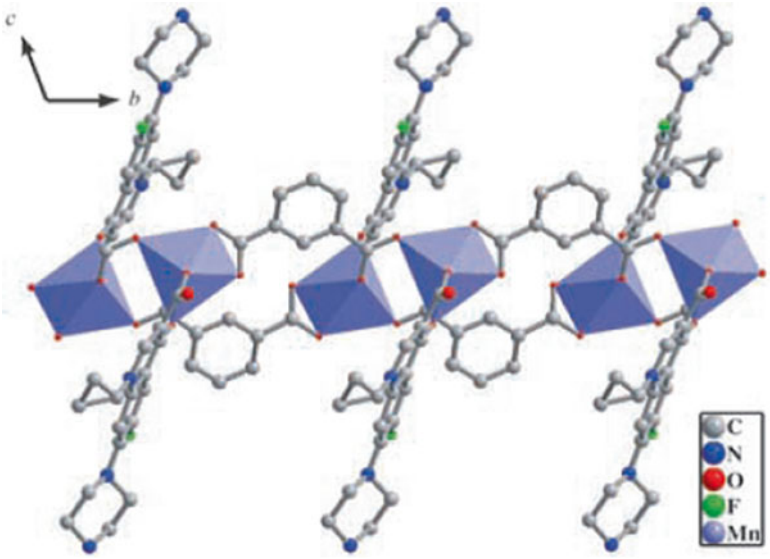


Fig. 7 Structure of complex, [Mn(cf)(1,3-bdc)] (Reproduced with permission of Wiley [369])

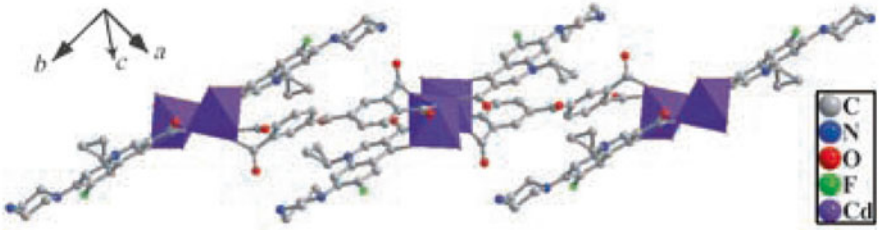


Fig. 8 Supramolecular structure of ciprofloxacin complex, $[Cd_2(cf)_2(bptc)(H_2O)_2]\cdot 8H_2O$ (bptc = 3,3′,4,4′-benzophenontetracarboxylate) (Reproduced with permission of Wiley [369])

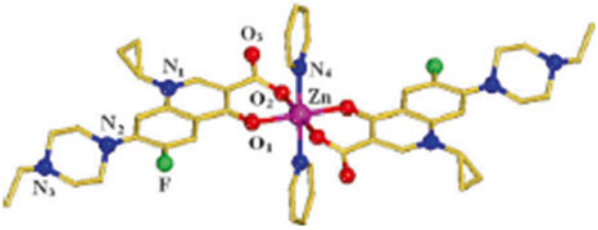
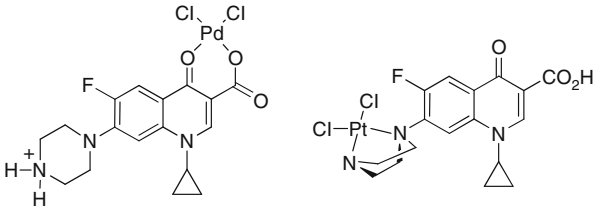


Fig. 9 Structure of complex $[Zn(erx)_2(py)_2]\cdot 6H_2O\cdot MeOH$ (Reproduced with permission of Elsevier [371])

One of the modern trend in the chemistry of fluoroquinolones is the formation of Pd(II) and Pt(II) complexes with a number of fluoroquinolones, such as ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin and gatifloxacin [375, 376]. Two examples are given below Scheme 62.



Scheme 62 Pd(II) and Pt(II) complexes of fluoroquinolones

A great deal of complexes derived from enoxacin, norfloxacin, lomefloxacin, fleroxacin, ofloxacin, rufloxacin, gatifloxacin and sparfloxacin and their luminescence properties of Tb^{3+}– and Eu^{3+}–complexes have been investigated (Fig. 10) [377]. Complexes of Tb^{3+}–enoxacin, Tb^{3+}–norfloxacin, Tb^{3+}– lomefloxacin and Tb^{3+}–fleroxacin were shown to display a relatively strong emission intensity compared with Tb^{3+}–ofloxacin, Tb^{3+}–rufloxacin, Tb^{3+}–gatifloxacin and Tb^{3+}– sparfloxacin. Quite weak peaks with unique characters of Eu^{3+} at 590 and 617 nm have been observed in the luminescence spectra of Eu^{3+}–enoxacin, however no luminescence of Eu^{3+} could be detected when Eu^{3+} was added to other fluoroquinolones. The distinct changes in emission intensities for Tb^{3+}–fluoroquinolone and Eu^{3+}–fluoroquinolone complexes might originate from different energy gaps between the triplet levels of fluoroquinolones and the excited levels of Ln^{3+}. Thus, research studies in the field of complexes of fluoroquinolones with metals are aimed at obtaining of biologically active coordination compounds, and also to use of complex formation for quantitative analysis of fluoroquinolones.

In conclusion it is worth noting that despite the successes reached in area of synthesis, studying of biological activity and application of fluoroquinolones, tasks of design of new structures, development of synthetic approaches, modifications of existing drugs by means of incorporation of substituents into positions 1–8 as well as annelation of additional rings to quinolone fragment continue to remain actual. Not less important studying of structure–activity relations among fluoroquinolones as in process of accumulation of such material all new dependences of antibacterial activity on positions and the nature of the substituents in a fluoroquinolone fragment become clear. The increasing attention is given to the synthesis of optically active isomers among fluoroquinolones and to their use as medicines. Fluoroquinolones are known to be not only antibacterial drugs, but also as compounds exhibiting other types of biological activity. Development of novel anticancer and antiviral agents in the series of fluoroquinolones is in progress. Researches in the field of metalocomplexes of fluoroquinolonecarboxylic acids directed to elucidation of “structure – bioactivity”

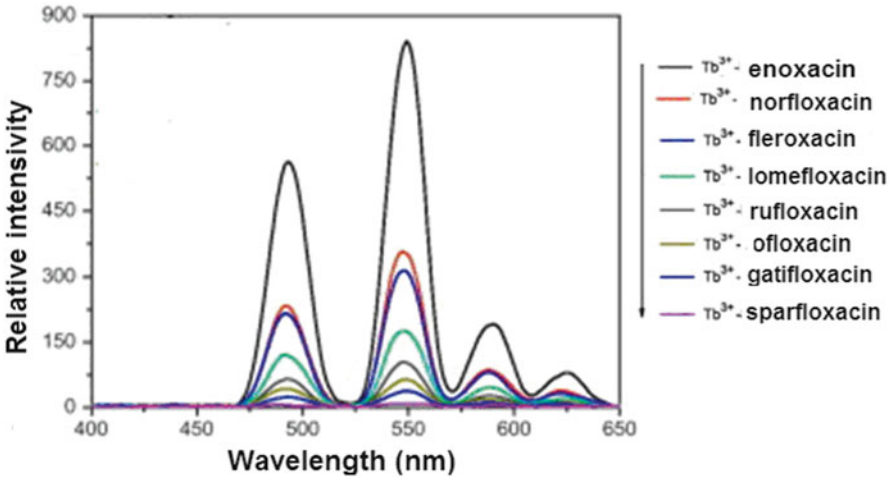


Fig. 10 Emission spectra of Tb^{3+}–complexes of some fluoroquinolones (Reproduced with permission of Elsevier [377])

relations and cation roles in interaction of fluoroquinolones with DNA are developed. Studying of complex formation of fluoroquinolones plays a crucial role for obtaining the fullest data on pharmacokinetic interaction of fluoroquinolones with other drugs.

References

1. Andriole T (ed) (1988) The quinolones. Academic Press, New York
2. Wolfson J, Hooper D (eds) (1989) Quinolone antimicrobial agents. American Society for Microbiology, Washington, DC
3. Siporin C, Heifetz C, Damaglia J (1990) The new generation of quinolones. Marcel Dekker Inc., New York
4. Mokrushina G, Alekseev S, Charushin V, Chupakhin O (1991) Zhurnal Vsesoyuznogo Khimicheskogo obschestva im. D.I. Mendeleeva 36:447–455
5. Chu D, Fernandes P (1991) Recent developments in the field of quinolone antibacterial agents. Adv Drug Res 21:39–144
6. Fadeeva N, Shul'gina M, Glushkov G (1993) Molecular and biological features of antibacterial action of derivatives 4-quinolon-3-carboxylic acids. Pharm Chem J 27:4–9
7. Mokrushina G, Charushin V, Chupakhin O (1995) Relationship between structure and antibacterial activity in the fluoroquinolone series of compounds. Pharm Chem J 29:590–606
8. Padeyskaya E, Yakovlev V (1995) Quinolones. Bioinform, Moscow
9. Andriole T (1998) The quinolones, 2nd edn. Academic Press, New York
10. Mokrushina G, Nosova E, Lipunova G, Charushin V (1999) Polycyclic fluoroquinolones. Russ J Org Chem 35:1447–1463
11. Hooper D, Rubinstein E (eds) (2003) Quinolone antibacterial agents. ASM Press, Washington, DC

12. Shams W, Evans M (2005) Guide to selection of fluoroquinolones in patients with lower respiratory tract infections. Drugs 65:949–991
13. Keam S, Croom K, Keating G (2005) Gatifloxacin: a review of its use in the treatment of bacterial infections in the US. Drugs 65:695–724
14. Bouzard D (1993) In: Krohn R, Kirst H, Maag H (eds) Antibiotics and antiviral compounds. Wiley, Weinheim
15. Hamada Y, Watanabe T, Umezu K (1999) Preparation of quinolinecarboxylic acid esters. JP Patent 11147875, 2 Jan 1999
16. Stankovic S, Mitov S, Stanojovic C (2003) A process for synthesis of antibiotic fluoroquinolinic acid derivatives. WO Patent 10144, 6 Feb 2003
17. Maslennikov E, Strunin B, Kalashnik V, Gusejnov F, Khaev E, Kovalev V (2003) Cyclocondensation method for preparing ethyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-3-quinolinecarboxylate from diethyl-2-(3-chloro-4-fluoroanilinometylenecarboxylate acid-Et ester. RU Patent 2206564, 20 June 2003
18. Chupakhin O, Charushin V, Rusinov V, Mokrushina G, Kotovskaya S, Baskakova Z, Kolmakova T (1996) Method for production of 1-ethyl-6-fluoro-7-(piperazinyl-1)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid. RU Patent 2054005, 10 Feb 1996
19. Azev Yu, Alekseev S, Charushin V, Rusinov V, Chupakhin O (1996) Process for preparing ethyl ester derivatives of 7-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. RU Patent 2052454, 20 Jan 1996
20. Chupakhin O, Charushin V, Mokrushina G, Kotovskaya S, Karpenko I, Karpin I, Petrova G, Sidjrjv E, Nefedov O, Volchkov N, Lipkind M, Shajdurov V, Zabolotskich V, Shipilov A, Tolstikov G, Gruzdev V, Navashin S, Fomina I (1992) Preparation of 1-ethyl-6-fluoro-7-(4-methylpiperazinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid. SU Patent 1766921, 7 Oct 1992
21. Dzhemilev U, Tolstikov G, Nefedov O, Chupakhin O, Charoshin V, Navashin S, Dokichev V, Sultanov S, Gruzdev V, Zverev V (1993) Preparation of ethyl 6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate. SU Patent 1786028, 7 Jan 1993
22. Richardson T, Shanbhag V, Adair K, Smith S (1998) Synthesis of 7-benzoxazol-2-yl and 7-benzothiazol-2-yl-6-fluoroquinolones. J Heterocycl Chem 35:1301–1304
23. Kumar N, Bhandari P (1997) A new process for the preparation of 1,4-dihydro-1-alkyl-6-fluoro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid derivatives. IN Patent 178696, 10 Feb 1997
24. Shin H, Chang J, Lee K (2005) One-pot four-step process for preparing 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid using DMF dialkyl acetals. WO Patent 40164, 6 May 2005
25. Gomez C, Villasante Prieto A, Francisko P (2005) One-pot process for preparing gatifloxacin. WO Patent 47260, 26 May 2005
26. Iki M, Ikemoto T, Sato T (2002) Process for preparing quinolinecarboxylic acid esters and 1,8-naphthyridinecarboxylic acid esters. JP Patent 155081, 28 May 2002
27. Lee T, Park N, Khoo J, Song S, An J (2004) Preparation of quinolonecarboxylate derivatives. WO Patent 56781, 8 July 2004
28. Wang Y, Chen R, Dong Z, Ben S, Nan H, Yu B, Zhao C (2002) Preparation of quinolone carboxylic acids. CN Patent 1338455, 6 Mar 2002
29. Randall J (2004) Preparation of quinoline derivatives as antibiotic intermediates using silylating agents for cyclization of ethoxy-substituted aromatic intermediates. WO Patent 13103, 14 Mar 2004
30. Muto M, Miura M, Kitagawa Y (2004) Process for the production of optically active quinolinecarboxylic acid and intermediates therefor. WO Patent 108680, 16 Dec 2004
31. Vales M, Lokshin V, Pepe G, Samat A, Guglielmetti R (2001) Enaminones acylation: competitive formation of quinolin-4-one and isoquinolin-1-one derivatives. Synthesis 2419–2426
32. Nishimura Y, Minamida A, Matsumoto K (1988) Synthesis and antibacterial activity of enoxacin analogues with a variant at position 1. Chem Pharm Bull 36:1223–1226

33. Ptaszynska K, Winiarski J, Zadelek S, Biedrzycki M, Dziegielewski K, Lewandowska B, Nowakowska K, Michalowska J (2004) Preparation alkyl-N-(2-fluoroethyl)-6,8-difluoro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinoline-carboxylate. Pol Patent 187824, 29 Oct 2004
34. Yoshikazu A, Kazuhiko I, Fujio I, Masaki H, Takayoshi I (2005) Synthesis and antibacterial activity of 1-(2-fluorovinyl)-7-substituted-4-quinolone-3-carboxylic acid derivatives, conformationally restricted analogues of fleroxacin. J Med Chem 48:3194–3202
35. Ritsumosa M, Sadahiro S (1994) Preparation of quinolinecarboxylic acids as intermediates for microbicides. JP Patent 0673013, 15 Mar 1994
36. Takemura M, Takahashi H, Sugita K, Miyauchi R (1998) Preparation of substituted cyclobutylamine derivatives as antibacterial agents. WO Patent 54169, 3 Dec 1998
37. Sheu J, Chen Y, Fang K, Wang T, Tzeng C, Peng C (1998) Synthesis and antibacterial activity of 1-(substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids and their 6,8-difluoro analogs. J Heterocycl Chem 35:955–964
38. Shindikar A, Viswanathan C (2005) Novel fluoroquinolones: design, synthesis, and in vivo activity in mice against *Mycobacterium tuberculosis* $H_{37}Rv$. Bioorg Med Chem Lett 15:1803–1806
39. Aizikovich A, Nikonov M, Kodess M, Korotayev V, Charushin V, Chupakhin O (2000) Novel 1-trifluoromethyl substituted 1,2-ethylenediamines and their use for the synthesis of fluoroquinolones. Tetrahedron 56:1923–1927
40. Hanessian S, Saladino R, Nunez Y (1996) On the binding site of quinolone antibacterials. An attempt to probe the shen model. Bioorg Med Chem Lett 6:2333–2338
41. Lucero B, Gomez C, Frugulhetti I, Faro L, Alvarenga L, de Souza M, de Souza T, Ferreira V (2006) Synthesis and anti-HSV-1 activity of quinolonic acyclovir analogues. Bioorg Med Chem Lett 16:1010–1013
42. Masoudi A, Iman A (2003) Synthesis and reactions of some New 6,7-dihaloquinolones bearing mercapto groups. Phosphorus Sulfur Silicon Relat Elem 178:2393–2402
43. Zheng H, Liu J, Zhang P (2010) One-pot synthesis and antimicrobial activity of novel quinolone heterocyclic derivatives. J Heterocycl Chem 47:1411–1414
44. Hong W, Lee K (2006) Baylis-Hillman route to several quinolone antibiotic intermediates. Synthesis 963–968
45. Dumas J, Khire U, Lasch S, Nagarathnam D, Scott W (2004) Preparation of quinolinecarboxylic acid derivatives and methods for use in treating cancer. WO Patent 80465, 21 Feb 2004
46. Khire U, Liu X, Nagaratham D, Wood J, Wang L, Wang L, Liu D, Zhao J, Guernon L, Zhang L (2005) Quinolinecarboxylic acid derivatives for treatment of hyperproliferative conditions, their preparation and pharmaceutical compositions. WO Patent 97752, 20 Oct 2005
47. Kuramoto Y, Ohshita Y, Yoshida J, Yazaki A, Shiro M, Koike T (2003) A novel antibacterial 8-chloroquinolone with a distorted orientation of the N1-(5-amino-2,4-difluorophenyl) group. J Med Chem 46:1905–1917
48. Gordeev M, Hackbarth C, Barbachyn M, Banitt L, Gage J, Luehr G, Gomez M, Trias J, Morin S, Zurenko G, Parker C, Evans J, White R, Patel D (2003) Novel oxazolidinone–quinolone hybrid antimicrobials. Bioorg Med Chem Lett 13:4213–4216
49. Yoon S, Chung Y, Lee C, Oh Y, Choi D, Kim N, Lim J, Jin Y, Lee D, Lee W (1997) Synthesis, pharmacokinetics, and biological activity of a series of new pyridonecarboxylic acid antibacterial agents bearing a 5-fluoro-2-pyridyl group or a 3-fluoro-4-pyridyl group at N-1. J Heterocycl Chem 34:1021–1027
50. Mealy N, Castaner J (2002) Quinolone antibacterial. Drug Future 27:1033–1038
51. Yoon S, Yong H, Lee C, Oh Yo, Choi D, Kim N (1995) Novel quinolinecarboxylic acid derivatives. WO Patent 5373, 23 Feb 1995
52. Yoshikazu A, Ichiro A, Kazuhiko I, Iinuma F, Hosaka N, Ishizaki T (2005) Synthesis and antibacterial activity of the 4-quinolone-3-carboxylic acid derivatives having a trifluoromethyl group as a novel N-1 substituent. J Med Chem 48:3443–3446
53. Jung J, Jung Y, Park O (2001) Synthesis of 4-hydroxyquinolin-2(1*H*)-one analogues and 2-substituted quinolone derivatives. J Heterocycl Chem 38:61–67
54. Jung J, Oh S, Kim W, Park W, Kong J, Park O (2003) Synthesis and biological properties of 4-substituted quinolin-2(1*H*)-one analogues. J Heterocycl Chem 40:617–623

55. Rao V, Wentrup C (2002) Synthesis of fluorinated 2-phenyl-4-quinolones from pyrrole-2,3-diones. J Chem Soc Perkin Trans I 1232–1235
56. Saloutin V, Bazyl' I, Skryabina Z, Aleksandrov G, Chupakhin O (1995) Crystalline hydrogen-bonded adducts of dimethyl sulphoxide and 7-hydroxypolyfluoroquinolones (chromones). J Fluorine Chem 74:15–18
57. Naik P, Chimatadar S, Nandibewoor S (2009) Kinetics and oxidation of fluoroquinoline antibacterial agent, norfloxacin, by alkaline permanganate: a mechanistic study. Ind Eng Chem Res 48:2548–2553
58. Pucci M, Ackerman M, Thanassi J, Shoen C, Cynamon M (2010) In vitro antituberculosis activities of ACH-702, a novel isothiazoloquinolone, against quinolone-susceptible and quinolone-resistant isolates. Antimicrob Agents Chemother 54:3478–3484
59. Molina-Torres C, Ocampo-Candiani J, Rendon A, Pucci M, Vera-Cabrera L (2010) *In vitro* activity of a new isothiazoloquinolone, ACH-702, against *Mycobacterium tuberculosis* and other mycobacteria. Antimicrob Agents Chemother 54:2188–2193
60. Marks K, Malik M, Mustaev A, Hiasa H, Drlika K, Kerns R (2011) Synthesis and evaluation of 1-cyclopropyl-2-thioalkyl-8-methoxy fluoroquinolones. Bioorg Med Chem Lett 21:4585–4588
61. Kondo H, Sakamoto F, Kawakami K, Tsukamoto G (1988) Studies on prodrugs. 7. Synthesis and antimicrobial activity of 3-formylquinolone derivatives. J Med Chem 31:221–225
62. Tanaka K, Houghton T, Kang T, Dietrich E, Delorme D, Ferreira S, Caron L, Viens F, Arhin F, Sarmiento I, Lehoux D, Fadhil I, Laquerre K, Liu J, Ostiguy V, Poirier H, Moeck G, Parr T, Far A (2008) Bisphosphonated fluoroquinolone esters as osteotropic prodrugs for the prevention of osteomyelitis. Bioorg Med Chem 16:9217–9229
63. Patel N, Patel A, Chauhan H (2007) Synthesis of amide derivatives of quinolone and their antimicrobial studies. Indian J Chem 46B:126–134
64. Patel N, Patel S, Patel J, Patel J, Corgamwala Y (2011) Synthesis and antibacterial activity of thioureido amide of fluoroquinolone. Int J Biol Chem 5:37–45
65. Srivastava S, Srivastava SK, Shukla A, Chauhan P, Puri S, Bhaduri A, Pandey V (1999) Synthesis and methemoglobin toxicity of the amides of 6/7 mono or disubstituted quinolone. Bioorg Med Chem Lett 9:25–30
66. Al-Soud Y, Al-Masoudi N (2003) A New class of dihaloquinolones bearing *N'*-aldehydoglycosylhydrazides, mercapto-1,2,4-triazole, oxadiazoline and α-amino ester precursors: synthesis and antimicrobial activity. J Brazilian Chem Soc 14:790–796
67. Patel N, Patel S (2009) Synthesis and antimicrobial activity of 2-phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-methylpiperazin-1-yl]-4-quinolone}carboxamido-3-thiazolidin-4-ones. Pharm Chem J 43:305–309
68. Sharad S, Ganesh M, Sunil G, Charnsingh G (2010) Green synthesis and biological evaluation of some novel azoles as antimicrobial agents. Bioorg Med Chem Lett 20:7200–7204
69. Obanin G, Fokin A, Ya B, Ryzhkov O, Skryabina Z, Saloutin V, Chupakhin O (2000) Synthesis of N-substituted 2-(5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin 3-yl)glyoxalic acids. Russ Chem Bull 49:1231–1236
70. Fokin A, Burgart Y, Ryzhkov O, Saloutin V (2001) Reactions of 1-aryl(alkyl)-3-ethoxalyl-5,6,7,8-tetrafluoro-1,4-d-hydrocinnolin(quinolin)-4-ones with aromatic dinucleophiles. Russ Chem Bull 50:689–692
71. Clark R, Wang S, Ma Z, Weitzberg M, Motter C, Tufano M, Wagner R, Gu Y, Dandliker P, Lerner C, Chovan L, Cai Y, Black-Schaefer C, Lynch L, Kalvin D, Nilius A, Pratt S, Soni N, Zhang T, Zhang X (2004) Novel inhibitors of bacterial protein synthesis: structure–activity relationships for 1,8-naphthyridine derivatives incorporating position 3 and 4 variants. Bioorg Med Chem Lett 14:3299–3302
72. Iones R, Barry A, Thomsberry C (1989) Antimicrobial activity of Ro 23-9424, a novel ester-linked codrug of fleroxacin and desacetylcefotaxime. Antimicrob Agents Chemother 33:944–950
73. Al-Hajjar F (2002) Preparation of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4-ones and derivatives as antibiotics. Eur Patent 1245566, 2 Oct 2002

74. Kerns R, Rybak M, Kaatz G, Vaka F, Cha R, Grucz R, Diwadkar V (2003) Structural features of piperazinyl-linked ciprofloxacin dimers required for activity against drug-resistant strains of *Staphylococcus aureus*. Bioorg Med Chem Lett 13:2109–2112
75. Park C, Lee J, Jung H, Kim M, Lim S, Yeo H, Choi E, Yoon E, Kim K, Cha J, Kim S, Chang D, Kwon D, Li F, Suh Y (2007) Identification, biological activity, and mechanism of the anti-ischemic quinolone analog. Bioorg Med Chem 15:6517–6521
76. Nguyen S, Ding X, Butler M, Tashjian T, Peet N, Bowlin T (2011) Preparation and antibacterial evaluation of decarboxylated fluoroquinolones. Bioorg Med Chem Lett 21:5961–5963
77. Vysokov V, Charushin V, Afanasyeva G, Chupakhin O (1993) The synthesis of fluorinated 4H-1,4-benzothiazine-2-carboxylic acid 1,1-dioxides – thionated analogues of Pefloxacin. Mendeleev Commun 3:159–160
78. Guo H, Qi J (2003) Preparation of 7-(aminomethyl-azaspiroheptyl)-quinoline-carboxylic acid derivatives as bactericides. WO Patent 14108, 20 Feb 2003
79. Saito T, Jouno T, Tani Y, Akiba T (2001) Process for producing quinolinecarboxylic acids and intermediates thereof. WO Patent 62734, 30 Aug 2001
80. Guo H, Liu J, Wang Y (2004) Preparation of 5-amino-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydroquinolin-4-one-3-carboxylic acid derivatives as antibacterial agents. CN Patent 1491944, 28 Apr 2004
81. Akiba T, Kitagawa Yu, Muto M (2003) Improved preparation of 5-acylamino-4-oxo-quinoline-3-carboxylic acids as bactericides and their intermediates. JP Patent 160567, 3 June 2003
82. Griffin J, Judice J (1999) Novel multi-binding therapeutic agents that modulate enzymatic processes. Patent 64037, 16 12 WO. 1999
83. Demuth T, White R (1997) 5-(N-Heterosubstituted amino)quinolone antimicrobials. US Patent 5646163, 8 July 1997
84. Hansen T, Gu Y, Rehm T, Dandliker P, Chovan L, Bui M, Nilius A, Beutel B (2005) Synthesis and antibacterial activity of 5-methoxy- and 5-hydroxy-6-fluoro-1,8-naphthyridone-3-carboxylic acid derivatives. Bioorg Med Chem Lett 15:2716–2719
85. Takahashi H, Mijauchi R, Itoh M, Takemura M, Hayakawa I (2002) Preparation of dehalogenoquinolinecarboxylic acid derivatives. WO Patent 40478, 25 May 2002
86. Cecchetti V, Fravolini A, Terni P Pagella P, Tabardini O (1993) 6-Aminopiperazinylquinolones and analogs, their synthesis and their use as antibacterial agents. Eur Patent 531958, 17 Mar 1993
87. Cecchetti V, Fravolini A, Palumbo M, Sissi C, Tabarrini O, Terni P, Xin T (1996) Potent 6-desfluoro-8-methylquinolones as new lead compounds in antibacterial chemotherapy. J Med Chem 39:4952–4957
88. Lawrence L, Wu P, Fan L, Gouveia K, Card A, Casperson M, Denbleyker K, Barrett J (2001) The inhibition and selectivity of bacterial topoisomerases by BMS-284756 and its analogues. J Antimicrob Chemother 48:195–201
89. Miyauchi R, Kawakami K, Ito M, Matsuhashi N, Ohki H, Inagaki H, Takahashi H, Takemura M (2009) Design, synthesis and biological evaluations of novel 7-[3-(1-aminocycloalkyl) pyrrolidin-1-yl]-6-desfluoro-8-methoxyquinolones with potent antibacterial activity against multi-drug resistant gram-positive bacteria. Bioorg Med Chem 17:6879–6889
90. Ruzic M, Pucelj J, Tomsic Z, Makuc S, Brne P, Barut M, Strancar A (2005) Process for preparing ciprofloxacin by contacting it with a novel support. WO Patent 75430, 18 Aug 2005
91. Niddam H, Dolitzky B, Pilarski G, Sterimbaum G (2004) Synthesis of gatifloxacin. WO Patent 69825, 19 Sep 2004
92. Mody S, Mehata B, Patel M, Shrikhande A, Mahajan R (1999) An improved process for the preparation of 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid and its salts. IN Patent 177148, 5 July 1999
93. Berthon-Cedille L, Leguern M (2008) Process for the preparation of fluoroquinolone-3-carboxylic acids via amination of alkyl fluoro(haloquinolone)carboxylates with amines. US Patent 54643, 28 Nov 2008
94. Himmler T, Jaetsch T, Hallenbach W, Rast H, Wetzstein H, Heinen E, Pirro F, Scheer M, Stegemann M, Stupp H (1998) Preparation of 7-(3-vinylpiperazin-1-yl)quinolinecarboxylic acid as antibacterials. DE Patent 19651687, 1 Jan 1998

95. Liu B, Yang C, Xu G, Zhu Y, Cui J, Wu X, Xie Y (2005) Syntheses of quinolone hydrochloride enantiomers from synthons (*R*)- and (*S*)-2-methylpiperazine. Bioorg Med Chem 13:2451–2458
96. Mulvihill M, Shaber S (2004) Chemical modification of drugs into labile derivatives with enhanced properties. US Patent 254182, 16 Dec 2004
97. Md-Saleh S, Chilvers E, Kerr K, Milner S, Snelling A, Weber J, Thomas G, Duhme-Klair A, Routledge A (2009) Synthesis of citrate–ciprofloxacin conjugates. Bioorg Med Chem Lett 19:1496–1498
98. Hayakama I, Atarashi S, Kimura E (1990) Preparation of 7-(azaspiroalkanyl)quinolonecarboxylates and analogs as bactericides. RU Patent 2094432, 7 Mar 1990
99. Rameshkumar N, Ashokkumar M, Subramanian E, Llavarasan R, Sridhar S (2003) Synthesis of 6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid derivatives as potential antimicrobial agents. Eur J Med Chem 38:1001–1004
100. Yun S, Jung Y, Lee S, Lee J (1997) Antimicrobial quinoline derivatives and process for the preparation thereof. KR Patent 9703501, 18 Mar 1997
101. Li Y, Lu R, Yang A, Zhang Y (2004) Synthesis of novel fluoroquinolone compounds. Heterocycl Commun 10:447–450
102. Foroumadi A, Emami S, Hassanzadeh A, Rajaee M, Sokhanvar K, Moshafi M, Shafiee A (2005) Synthesis and antibacterial activity of *N*-(5-benzylthio-1,3,4-thiadiazol-2-yl) and *N*-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl)piperazinyl quinolone derivatives. Bioorg Med Chem Lett 15:4488–4492
103. Foroumadi A, Mansouri S, Kiani Z, Rahmani A (2003) Synthesis and in vitro antibacterial evaluation of *N*-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolones. Eur J Med Chem 38:851–854
104. Chatterjee N, Bharat S, Naik S (1996) A process for the preparation of β-lactan antibiotic linked fluoroquinolones as hybrid antibacterial agents. IN Patent 180479, 11 Apr 1996
105. Zhi C, Wright G (2003) Preparation of uracils and related compounds as antibacterials that inhibit bacterial DNA polymerase III C and type II bacterial topoisomerase. US Patent 181719, 25 Sep 2003
106. Zhi C, Long Z, Manikowski A, Comstock J, Xu W, Brown N, Tarantino P, Karsten J, Holm A, Dix E, Wright G, Barnes M, Butler M, Foster K, LaMarr W, Bachand B, Bethell R, Cadilhac C, Charron S, Lamothe S, Motorina I, Storer R (2006) Hybrid antibacterials. DNA polymerase–topoisomerase inhibitors. J Med Chem 49:1455–1465
107. Zhi C. Wright G (2002) Preparation of uracils and related compounds as antibacterials that inhibit bacterial DNA polymerase III C and type II bacterial topoisomerase. WO Patent 102792, 27 Dec 2002
108. Darehkordi A, Javanmiri M, Ghazi S, Assar S (2011) Synthesis of *N*-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone derivatives and their antibacterial evaluations. J Fluorine Chem 132:263–268
109. Hutschiterlen G, Specklin J, Baeschlin D, Lochev H, Sigwalt C (2004) Preparation and use of oxazolidinone-quinolinone and oxazolidinone-naphthyridinone hybrid antibiotics for the treatment of anthrax and other infections. WO Patent 96221, 12 Jan 2004
110. Ellsworth E, Hutchings K, Murphy S, Powell S, Sciotti R, Tran T (2005) Synthesis of azetidinyl quinolones as antibacterial agents. WO Patent 26146, 24 Mar 2005
111. Kato N, Iwasaki N, Azuma T (2000) Preparation of antibacterial 5-amino-8-methyl-7-pyrrolidinylquinoline-3-carboxylic acids and their intermediates. JP Patent 247970, 12 Sep 2000
112. Takahashi H, Ruroyanagi J, Miyauchi R, Nagamochi M, Takemura M, Hayakawa I (2005) Preparation of quinoline compounds containing pyrrolidine moiety as antibacterial agents. WO Patent 111015, 24 Nov 2005
113. Takemura M, Takahashi H, Ohki H, Kimura K, Miyauchi R, Takeda T (1998) Preparation of cis-substituted fluoromethylpyrrolidine derivatives of 1,4-dihydro-4-oxoquinoline-3-carboxylic acid as antibacterial agents. WO Patent 58923, 30 Dec 1998
114. Ellsworth E, Tayler C, Murphy S, Ranckhorst M, Starr J, Hutchings K, Limberakis C, Hoyer D (2005) Preparation of quinoline antibacterial agents. WO Patent 49602, 2 June 2005
115. Kim B (2001) A process for preparation of pyrrolidino-quinolinecarboxylic acid derivatives (e.g. gemifloxacin) with improved filtration. WO Patent 68649, 20 Sep 2001

116. Hong C, Kim Y, Lee Y, Kwak J (1998) Methyloxime-substituted aminopyrrolidine: a new surrogate for 7-basic group of quinolone. Bioorg Med Chem Lett 8:221–226
117. Hong C, Kim Y, Kim S, Chang J, Choi H, Nam D, Kim A, Lee J, Park K (1998) Preparation of quinoline (or naphthyridine)-3-carboxylic acids such as 7-(4-aminomethyl-3-mrthyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid as antibacterials. US Patent 5776944, 7 July 1998
118. Choi H, Choi S, Nam D, Choi B (2003) Improved two-step process for preparing acid salts of gemifloxacin via Schiff-base protected intermediates. WO Patent 87100, 23 Oct 2003
119. Choi D, Shin J, Yang J, Yoon S, Jung Y (2004) Syntheses and biological evaluation of new fluoroquinolone antibacterials containing chiral oxiimino pyrrolidin. Bioorg Med Chem Lett 14:1273–1277
120. Lv K, Liu M, Feng L, Sun L, Sun Y, Wei Z, Guo H (2012) Synthesis and antibacterial activity of naphthyridone derivatives containing mono/difluoro-methyloxime pyrrolidine scaffolds. Eur J Med Chem 47:619–625
121. Nakayama T (2004) Preparation of intermediates for antibacterial quinoline-carboxylic acids. JP Patent 244380, 14 Feb 2004
122. Naoki O, Toshifumi A (2003) Process for producing antibacterial quinolone-carboxylic acid derivatives. WO Patent 97634, 10 Sep 2003
123. Kimura Y, Atarashi S, Kawakami K, Sato K, Hayakawa I (1994) Fluorocyclopropyl)quinolones. 2. Synthesis and stereochemical structure-activity relationships of chiral 7-(7-amino-5-azaspiro[2.4]heptan-5-yl)-1-(2-fluorocyclopropyl)quinolone antibacterial agents. J Med Chem 37:3344–3352
124. Yoon S, Chung Y, Lee C, Oh Y, Kim N, Lim J, Jin Y (1999) Preparation and antibacterial activity of quinolone carboxylic acid derivatives. WO Patent 00393, 12 Jan 1999
125. Feng L, Liu M, Wang S, Chai Y, Lv K, Shan G, Cao J, Li S, Guo H (2011) Synthesis of naphthyridone derivatives containing 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds. Tetrahedron 67:8264–8270
126. Petersen U, Schenke T, Krebs A, Grohe K, Schriewer M, Haller I, Metzger K, Endermann R, Zeiler H (1997) Preparation of 7-(1-pyrrolidinyl)-3-quinolonecarboxylic acids and naphthyridine-3-carboxylic acids as antimicrobial agents and feed additives. US Patent 5607942, 4 Mar 1997
127. Inagaki H, Miyauchi S, Miyauchi R, Kawato H, Ohki H, Matsuhashi N, Kawakami K, Takahashi H, Takemura M (2003) Synthesis and structure–activity relationships of 5-amino-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-8-methylquinolonecarboxylic acid antibacterials having fluorinated 7-[(3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidin-1-yl] substituents. J Med Chem 46:1005–1015
128. Inagaki H, Takeda T, Miyauchi R, Kawakami K, Takahashi H, Takemura M (2004) Practical synthesis of DQ-113, a new quinolone antibacterial agent, by using the intramolecular Horner-Wadsworth-Emmons reaction. Heterocycles 63:699–706
129. Muto M, Kitagawa Y (2004) Process for preparation of quinolinone derivatives. WO Patent 113321, 29 Dec 2004
130. Asahina Y, Takei M (2005) Preparation of quinolonecarboxylic acid derivatives as antibacterial agents. Eur Patent 1666477, 24 Mar 2005
131. Ellsworth E, Murphy S (2005) Preparation of quinolone derivatives as antibacterial agents. WO Patent 111030, 24 Nov 2005
132. Park T, Lee S, Han Ch (2002) Preparation of pyridinyl (pyrrolidinyl) quinolone carboxylates as antimicrobials. US Patent 130302, 20 Nov 2002
133. Asahina J, Takei M (2005) Preparation of quinolonecarboxylic acid derivatives as antibacterial agents. WO Patent 26147, 24 Mar 2005
134. Ellsworth E, Sciotti R, Stark J (2005) Preparation of pyrrolidinylquinolones as antibacterials. WO Patent 26165, 24 Mar 2005
135. Hubschwerlen C, Specklin J, Surivet J, Baeschlin D (2005) Preparation of oxazolidinones-quinolinones as hybrid antibiotics. WO Patent 23801, 17 Mar 2005
136. De Souza N, Patel M, Deshpande P, Agarwal S, Sreenivas K, Nair S, Chugh Ya, Shukla M (2003) Preparation of chiral, broad-spectrum antimicrobial 7-substituted piperidino quino-

lone carboxylic acids derivatives effective against multidrug-resistant bacteria. US Patent 216568, 20 Nov 2003
137. Hilty P, Hubschwerlen C, Thomas A (2001) Expeditious solution phase synthesis of fluoroquinolone antibacterial agents using polymer supported reagents. Tetrahedron Lett 42:1645–1646
138. Ganapati Reddy P, Baskaran S (2001) Microwave assisted amination of quinolone carboxylic acids: an expeditious synthesis of fluoroquinolone antibacterials. Tetrahedron Lett 42:6775–6777
139. Deshpande V, Ravindvanathan T (2000) An improved process for the preparation of ciprofloxacin. IN Patent 184650, 16 Nov 2000
140. Hu X, Kim N, Gray J, Almstead J, Seibel W, Ledoussal B (2003) Discovery of (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones as potent antibacterial agents with a broad spectrum of activity and activity against resistant pathogens. J Med Chem 46:3655–3661
141. Ledaussal B, Alnstead J, Grey J, Hu X (1999) Preparation of quinolones as antimicrobials. US Patent 6329391, 25 Mar 1999
142. Bowers GE, Macielag MJ, Xu X, Paget S, Weidner W (2005) Preparation of 7-(alkylidene-substituted-heterocyclic amino) quinolones and naphthyridones as bactericides. WO Patent 33108, 14 Apr 2005
143. Chai Y, Liu M, Wang B, You X, Feng L, Zhang Y, Cao J, Guo H (2010) Synthesis and in vitro antibacterial activity of novel fluoroquinolone derivatives containing substituted piperidines. Bioorg Med Chem Lett 20:5195–5198
144. Chai Y, Wang B, Liu M, Yi H, Sun L, You X, Guo H (2011) Design, synthesis and in vitro antibacterial activity of 7-(4-alkoxyimino-3-aminomethylpiperidin-1-yl)fluoroquinolone derivatives. Bioorg Med Chem Lett 21:3377–3380
145. Zhang Y, Li G, Liu M, You X, Feng L, Lv K, Cao J, Guo H (2011) Synthesis and in vitro antibacterial activity of 7-(3-alkoxyimino-5-amino/methylaminopiperidin-1-yl)fluoroquinolone derivatives. Bioorg Med Chem Lett 21:928–931
146. Huang X, Zhang A, Chen D, Jia Z, Li X (2010) 4-Substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine: novel C7 moieties of fluoroquinolones as antibacterial agents. Bioorg Med Chem Lett 20:2859–2863
147. Chiu C, Lewin T (1999) Process for preparing naphthyridones and intermediates. Eur. Patent 930297, 21 July1999
148. Okada H, Chiba K, Nakada K (1997) Preparation of pyridonecarboxylic acids and their use as antibacterial agents against Helibacter. JP Patent 9208578, 12 Aug 1997
149. Anquetin G, Rouquayrol M, Mahmoudi N, Santillana-Hayat M, Gozalbes R, Greiner J, Farhati K, Derouin F, Guedj R, Vierling P (2004) Synthesis of new fluoroquinolones and evaluation of their in vitro activity on *Toxoplasma gondii* and *Plasmodium* spp. Bioorg Med Chem Lett 14:2773–2776
150. Vilsmaier E, Goerz T (1998) Diastereoselective syntheses of *N*-protected derivatives of 1α,5α,6β-6-amino-3-azabicyclo[3.1.0]hexane; a route to trovafloxacin 6β-diastereomer. Synthesis 1998(5):739–744
151. Ota N, Shirono T, Akiba T (2003) Process for preparing of quinolinecarboxylic acid derivatives. JP Patent 96075, 3 Apr 2003
152. De Souza N, Patel M, Gupta S, Upadhyay D, Shukla M, Chaturvedi N, Bhawsar S, Nair S, Jafri M, Khozakiwala H (2002) Preparation and use of quinolone and naphthyridine derivatives as inhibitors of cellular efflux pumps of microbes. WO Patent 9758, 7 Feb 2002
153. Hagen S, Josyula V, Venkata N (2005) Preparation of substituted quinolones and derivatives there of as antibacterial agents. WO Patent 26161, 24 Mar 2005
154. Huang X, Chen D, Wu N, Zhang A, Jia Z, Li X (2009) The synthesis and biological evaluation of a novel series of C7 non-basic substituted fluoroquinolones as antibacterial agents. Bioorg Med Chem Lett 19:4130–4133
155. Norris T, Braish T, Butters M, DeVries K, Hawkins J, Massett S, Rose P, Santafianos D, Sklavounos C (2000) Synthesis of trovafloxacin using various (1α,5α,6α)-3-azabicyclo[3.1.0] hexane derivatives. J Chem Soc Perkin Trans 1 2000:1615–1622
156. Norris T (2000) Preparation of trovafloxacin and analogs. Eur. Patent 976749, 2 Feb 2000

157. Inagaki H, Takahashi H, Takemura M (2004) Synthesis and antibacterial activity of novel 6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-4-oxoquinoline-3-carboxylic acids bearing cyclopropane-fused 2-amino-8-aza-bicyclo[4.3.0]nonan-8-yl substituents at the C-7 position. Bioorg Med Chem Lett 14:5193–5198
158. Himmer T, Rast H (2000) Semihydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid. DE Patent 19854357, 31 May 2000
159. Himmer T, Hallenbach W, Rast H (2000) Crystal modification A of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. DE Patent 19854356, 31 May 2000
160. Himmer T, Hallenbach W, Rast H (2000) Crystal modification B of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid. DE Patent 19854355, 31 May 2000
161. Guo H, Liu J (2005) Preparation of quinolonecarboxylic acid derivative as antibiotics. WO Patent 103048, 3 Nov 2005
162. Matzke M, Petersen U, Jaetsch T, Bartel S, Schenke T, Himmler T, Baasner B, Werling H, Scharler K, Labischinski H (1998) Preparation of 7-(2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl) quinolone- and naphthyridinecarboxylic acid derivatives for therapy of *Helicobacter pylori* infections and associated gastroduodenal illnesses. DE Patent 19652239, 18 June 1998
163. Bhushan L, Bhushan L, Kumar S (2005) Preparation of quinolones as novel antiinfective compounds. WO Patent 19224, 3 Mar 2005
164. Nagibina N, Sidorova L, Klyuev N, Carushin V, Chupakhin O (1997) Application of 1,3-dipolar cycloaddition methodology for the synthesis of novel fluoroquinolones. Russ J Org Chem 33:1468–1475
165. Nagibina N, Charushin V, Sidorova L, Klyuev N (1998) Molecular rearrangement of 1,2,3-triazolines – adducts of 7-azido-6-fluoroquinolone-4 with alkenes. Russ J Org Chem 34:434–446
166. Mochulskaya N, Charushin V, Sidorova L, Chupakhin O, Tkachev A (2000) Azomethinoxide fragment in the structure modification of fluoroquinolones. Russ J Org Chem 36:1800–1808
167. Mochulskaya N, Sidorova L, Charushin V (2002) Three-component cyclization of hydroxylamino-substituted quinoline with reactive methylene compounds and formaldehyde: new method for the synthesis of 7-(isoxazolidin-2-yl)-6-fluoroquinolones. Russ Chem Bull 51:2106–2108
168. Leyva S, Leyva E (2007) Thermochemical reaction of 7-azido-1-ethyl-6,8-difluoroquinolone-3-carboxylate with heterocyclic amines. An expeditious synthesis of novel fluoroquinolone derivatives. Tetrahedron 63:2093–2097
169. McPherson J, Runner R, Buxton T, Hartmann J, Farcasiu D, Bereczki L, Roth E, Tollas S, Ostorhazi E, Rozgonyi F, Herczegh P (2012) Synthesis of osteotropic hydroxybisphosphonate derivatives of fluoroquinolone antibacterials. Eur J Med Chem 47:615–618
170. Yasumichi F, Masanori T, Yoshkazu A, Sato T, Kurasaki H, Ebisu H, Takei M, Fukuda H (2008) Preparation of mutilin derivatives containing heterocyclic aromatic carboxylic acid moiety at 14-position. Eur Patent 2149571, 27 Nov 2008
171. Elmore S, Cooper C, Schultz C, Hutchinson D, Donner P, Green B, Anderson D, Xie Q, Dinges J, Lynch L (2001) Quinoline- and naphthyridinecarboxylic acid antibacterials. WO Patent 32655, 10 May 2001
172. Zhang X, Mu F, Robinson B, Wang P (2010) Concise route to the key intermediate for divergent synthesis of C7-substituted fluoroquinolone derivatives. Tetrahedron Lett 51:600–601
173. Zang Z, Zhou W (2005) Arylation of nitromethane: masked nucleophilic formylation of fluoroquinolones. Tetrahedron Lett 46:3855–3858
174. Zang Z, Zhou W, Yu A (2004) Synthesis and antibacterial activity of 7-(substituted)aminomethyl quinolones. Bioorg Med Chem Lett 14:393–395
175. Zhu B, Marinelli B, Goldschmidt R, Foleno B, Hilliard J, Bush K, Macielag M (2009) Synthesis and antibacterial activity of 7-(1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl) quinolones. Bioorg Med Chem Lett 19:4933–4936

176. Takemura M, Kimura Y, Takahashi H, Ishida Y (1998) Preparation and formulation of aminocyclopropylpyrrolidinylquinolone derivatives as bactericides. Eur Patent 0919553, 22 Jan 1998
177. Tang X, Tang X (2004) Preparation of gatifloxacin hydrobromide and application antibacterial agents. CN Patent 1548435, 24 Nov 2004
178. Ravikumar K, Sridhar B (2006) Moxifloxacinium chloride–water–methanol (2/1/1), a novel antibacterial agent. Acta Crystallogr C 62:478–482
179. Keating G, Scott L (2004) Moxifloxacin: a review of its use in the management of bacterial infections. Drugs 64:2347–2377
180. Xiao Y, Yong D, Li L, Liang Q, Chang Ya, Chen Yu, Lu X, Ye Z (2003) Process for the preparation of gatifloxacin. CN Patent 1461748, 17 Dec 2003
181. Lee E, Chris L, Bentlej T (2005) Preparation of quinolone antibacterial agents. WO Patent 26145, 24 Mar 2005
182. De Souza N, Patel M, Deshpande P, Agarwal S, Gupte S, Upadhyay D, Bhawsar S, Beri R, Sreenivas K, Nair S, Sheela C, Shukla M, ChughY, Shetty N, Yeole R, Reddy M (2002) Preparation of chiral broad-spectrum antimicrobial 7-substituted piperidinoquinolinecarboxylic acid derivatives. WO Patent 85886, 31 Oct 2002
183. Deshpande P, Bhavsar S, Chugh Y, Yeole R, De Souza N, Patel M (2005) Novel polymorphs of racemic dextrorotatory and levorotatory enantiomers of 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and hydrochloride and mesylate salts. WO Patent 66154, 21 July 2005
184. Takahashi H, Hagiwara T, Hayakawa I (2002) Preparation of fluoroquinoline drug with reduced effect on the heart. WO Patent 76458, 3 Oct 2002
185. Schriewer M, Grohe K, Krebs A, Petersen U, Schenke T, Haller I, Metzger K, Endermann R, Zeiler H (1992) Antibacterial 5-alkylquinolinecarboxylic acids. US Patent 5140033, 18 Aug 1992
186. Takemura M, Kimura Y, Takahashi H, Kimura K, Miyauchi S, Ohki H, Sugita K, Miyauchi R (2000) Preparation of *cis*-substitutedaminocycloalkylpyrrolidine derivatives of 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids as antimicrobial drugs. US Patent 6121285, 19 Sep 2000
187. GehringR,MohrsK,HeilmannW,DiehlH(1997)Preparationof8-methoxyquinolonecarboxylates. DE Patent 19751948, 24 Nov 1997
188. Ochi K, Shimizu H (1993) Preparation of 6-fluoro-7-(heterocyclic amino)-3-quinolonecarboxylic acid derivatives as intermediates for antimicrobial agents. US Patent 5869661, 2 May 1993
189. Takahashi H, Miyauchi R, Takemura M (2005) Preparation of 8-cyanoquinolone-carboxylic acid derivatives as antibacterial agents. WO Patent 30752, 7 Apr 2005
190. Bartel S, Jaetsch T, Himmler T (1997) 8-Cyano-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0] nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid derivatives. WO Patent 31001, 28 Aug 1997
191. Stepanchikova A, Lagunin A, Filimonov D, Poroikov V (2003) Prediction of biological activity spectra for substances: evaluation on the diverse sets of drug-like structures. Curr Med Chem 10:225–233
192. Lagunin A, Zakharov A, Filimonov D, Poroikov V (2007) A new approach to QSAR modelling of acute toxicity. SAR QSAR Environ Res 18:285–298
193. Lei B, Xi L, Li J, Liu H, Yao X (2009) Global, local and novel consensus quantitative structure-activity relationship studies of 4-(phenylaminomethylene) isoquinoline-1, 3 (2*H*, 4*H*)-diones as potent inhibitors of the cyclin-dependent kinase 4. Anal Chim Acta 644:17–24
194. Li X, Zhu Z, Cheng X, Yang X (2007) Quantitative structure-pharmacokinetic/pharmacodynamic relationship for fluoroquinolones. Chem Pharm J 41:23–28
195. Wagman A, Wentland M (2007) In: Taylor J, Triggle D (eds) Comprehensive medicinal chemistry II. Elsevier, Oxford
196. Bryskier A (2005) In: Bryskier A (ed) Antimicrobial agents. ASM Press, Washington, DC
197. Dalhoff A, Schmitz F (2003) In vitro antibacterial activity and pharmacodynamics of new quinolones. Eur J Clin Microbiol Infect Dis 22:203–207
198. Al-Trawneh S, Zahra J, Kamal M, El-Abadelah M, Zani F, Incerti M, Cavazzoni A, Alfieri R, Petronini P, Vicini P (2010) Synthesis and biological evaluation of tetracyclic fluoroquinolones as antibacterial and anticancer agents. Bioorg Med Chem Lett 18:5873–5884

199. Emami S, Shafiee A, Foroumadi A (2006) Structural features of new quinolones and relationship to antibacterial activity against gram-positive bacteria. Mini-Rev Med Chem 6:375–386
200. Boteva A, Krasnykh O (2009) The methods of synthesis, modification and biological activity of 4-quinolones. Chem Het Comp 45:757–785
201. Chu D (1985) Preparation of benzoxazoloquinolines as antibacterial agents ZA Patent 02802, 27 Nov 1985
202. Lipunova G, Nosova E, Vasil'eva P, Charushin V (2003) Fluorinated benzimidazo[1,2-a]quinolones. Russ Chem Bull 52:457–460
203. Saloutin V, Burgart Y, Chupakhin O (2002) Fluorinated tricarbonyl compounds. UrO RAN, Ekaterinburg
204. Barrett D, Sasaki H, Kinoshita T, Sakane K (1996) A novel [3 + 2] annulation: synthesis and X-ray crystallographic structure of a novel tetrahydropyrazolo[1,5-*a*]quinoline, an intermediate towards new tricyclic quinolone antibacterials. J Chem Soc Chem Commun 61–62
205. Barrett D, Sasaki H, Kinoshita T, Tsutsumi H, Sakane K (1996) Alkylation of 1-[*N* -(hydroxymethyl)- *N* -methylamino]-4-quinolones. An improved preparation of intermediates for novel potent tricyclic quinolone antibacterial agents. Bull Chem Soc Jp 69:1371–1375
206. Tsoi E, Charushin V, Nosova E, Lipunova G, Tkachev A (2001) New approach to [*a*]-fused fluoroquinolones: the synthesis of 5-oxo-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolines. Mendeleev Commun 11:53–55
207. Edmont D, Marot C, Chenault J (2002) Synthesis of novel fused tricyclic quinolones: 4*a*,5-dihydro-1H-[1;2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-triones. J Heterocycl Chem 39:1161–1167
208. Edmont D, Chenault J (2003) 8-Fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]-quinoline-1,6(2*H*)-dione: synthesis and reactivity. J Heterocycl Chem 40:789–793
209. Edmont D, Chenault J (2001) A convenient selective *N*-alkylation of 4-Oxo-1,4-dihydro-2-quinoline carboxylic acid. Synlett 6:833–837
210. Azev Y, Shorshnev S, Gabel' D, Dul'ks T (2003) Intramolecular thermal condensation of 3-acetyl-5-oxopyrazolo[1,5-a]quinoline-4-ethylcarboxylate: a simple pathway to the new tetracyclic system containing fluoroquinolone fragment. Pharm Chem J 37:327–328
211. Gao Y (2004) Preparation of prulifloxacin from 3,4-difluoroaniline and 3-hydroxy-2-butanone. CN Patent 1478781, 3 Mar 2004
212. Segawa J, Kazuno K, Matsuoka M, Amimoto I, Ozaki M, Matsuda M, Tomii Y, Kitano M, Kise M (1995) Studies on pyridonecarboxylic acids. IV. Synthesis and antibacterial activity evaluation of S-(-)- and R-(+)-6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4H-[1,3]thiazeto-[3,2-a]quinoline-3-carboxylic acids. Chem Pharm Bull 43:1238–1240
213. Segawa J, Kazuno K, Matsuoka M, Shiranase I, Ozaki M, Matsuda M, Tomii Y, Kitano M, Kise M (1995) Studies on pyridonecarboxylic acids. III. Synthesis and antibacterial activity evaluation of 1,8-disubstituted 6-fluoro-4-oxo-7-piperazinyl-4H-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives. Chem Pharm Bull 43:63–70
214. Petersen U, Matzke M, Jaetsch T, Schenke T, Himmler T, Bartel S, Baasner B, Werling H, Schaller K, Labischinski H, Endermann R (1998) Use of 7-(1-aminomethyl-2-oxa-7-azabicyclo[3.3.0.]oct-7-yl)quinolonecarboxylates, naphthyridinones and related compounds for *Helibacter pylori* infection therapy and associated gastroduodenalillinesses. DE Patent 19652219, 18 June 1998
215. Matsuoka M, Segawa J, Makita Y (1997) Studies on pyridonecarboxylic acids. V. A practical synthesis of ethyl 6,7-difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate, a key intermediate for the new tricyclic quinolone, prulifloxacin (NM441) and versatile new syntheses of the 2-thioquinoline skeleton. J. Heterocycl Chem 34:1773–1779
216. Keam S, Perry C (2004) Prulifloxacin. Drugs 64:2221–2234
217. Matsuoka M, Segawa J, Aminito I, Masui Y, Tomii Y, Kitano M, Kise M (1999) Synthesis and antibacterial activity of novel 7-substituted 6-fluoro-1-methylene-4-oxo-4*H*-[1,3] thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives. Heterocycles 51:2915–2930
218. Petersen U, Schenke T, Saetsch T, Bartel S, Bremm K, Endermann R, Metzger K (1994) Preparation of quinolone and naphthyridine carboxylic acid-derivative antibiotics. DE Patent 4427530 4 Aug 1994

219. Cecchetti V, Cruciani G, Filipponi E, Fravolini A, Tabarrini O, Xin T (1997) Synthesis and antibacterial evaluation of [1,3]benzothiazino[3,2-*a*]quinoline- and [3,1]benzothiazino[1,2-a]quinoline-6-carboxylic acid derivatives. Bioorg Med Chem 5:1339–1344
220. Wiles J, Song Y, Wang Q, Lucien E, Hashimoto A, Cheng J, Marlor C, Ou Y, Podos S, Thanassi J, Thoma C, Deshpande M, Pucci M, Bradbury B (2006) Biological evaluation of isothiazoloquinolones containing aromatic heterocycles at the 7-position: in vitro activity of a series of potent antibacterial agents that are effective against methicillin-resistant *Staphylococcus aureus*. Bioorg Med Chem Lett 16:1277–1281
221. Wiles J, Hashimoto A, Thanassi J, Cheng J, Incarvito C, Deshpande M, Pucci M, Bradbury B (2006) Isothiazolopyridones: synthesis, structure, and biological activity of a new class of antibacterial agents. J Med Chem 49:39–42
222. Bradbury B, Deshphande M, Pucei M, Wang Q, Wiles J, Song M, Hashimoto A, Lucien E (2005) Preparation of isothiazoloquinolones and related compounds as antiinfective agents. WO Patent 19228, 3 Mar 2005
223. Wiles J, Wang Q, Lucien E, Hashimoto A, Song Y, Cheng J, Marlor C, Ou Y, Podos S, Thanassi J, Thoma C, Deshpande M, Pucci M, Bradbury B (2006) Isothiazoloquinolones containing functionalized aromatic hydrocarbons at the 7-position: synthesis and *in vitro* activity of a series of potent antibacterial agents with diminished cytotoxicity in human cells. Bioorg Med Chem Lett 16:1272–1276
224. Hashimoto A, Pais G, Wang Q, Lucien E, Incarvito C, Deshpande M, Bradbury B, Wiles J (2007) Practical synthesis and molecular structure of a potent broad-spectrum antibacterial isothiazoloquinolone. Org Process Res Dev 11:389–398
225. Wang Q, Lucien E, Hashimoto A, Pais G, Nelson D, Song Y, Thanassi J, Marlor C, Thoma C, Cheng J, Podos S, Ou Y, Deshpande M, Pucci M, Buechter D, Bradbury B, Wiles J (2007) Isothiazoloquinolones with enhanced antistaphylococcal activities against multidrug-resistant strains: effects of structural modifications at the 6-, 7-, and 8-positions. J Med Chem 50:199–210
226. Kim H, Wiles J, Wang Q, Pais G, Lucien E, Hashimoto A, Nelson D, Thanassi J, Podos S, Deshpande M, Pucci M, Bradbury B (2011) Exploration of the activity of 7-pyrrolidino-8-methoxyisothiazoloquinolones against methicillin-resistant *Staphylococcus aureus* (MRSA). J Med Chem 54:3268–3282
227. Kawamura K, Michara S, Nukii S, Uchida I (2003) Preparation of 1-methyl-1,4-dihydro-9H-pyrazolo[4,3-b]-quinoline-9-one derivatives as protein kinase C inhibitors. JP Patent 55376, 26 Feb 2003
228. Fujita M, Egawa H, Kataoka M, Miyamoto T, Nakano J, Matsumoto J (1995) Imidazo- and triazoloquinolones as antibacterial agents. Synthesis and structure-activity relationships. Chem Pharm Bull 43:2123–2132
229. Fujita M, Egawa H, Miyamoto T, Nakano J, Matsumoto J (1996) 5-Alkoxyimidazoquinolones as potential antibacterial agents. Synthesis and structure-activity relationships. Chem Pharm Bull 44:987–990
230. Cooper C, Tufano M, Donner P, Chu D (1996) The synthesis and in vitro antibacterial activity of conformationally restricted quinolone antibacterial agents. Bioorg Med Chem 4:1307–1315
231. Yusuf M, Monther A, Khanfar A, Shuheil M, Ei-Abadelah M, Boese R (2006) Heterocycles [*h*]fused onto 4-oxoquinolines. Part I. Synthesis of 6-Oxo-6,9-dihydro[1,2,5]oxadiazolo[3,4-h]quinoline-7-carboxylic acid *N*-oxide. Heterocycles 68:1163–1172
232. Al-Qawasmeh R, Zahra J, Zani F, Vicini P, Boese R, El-Abadelah M (2009) Synthesis and antibacterial activity of 9-cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-[1,2,5]thiadiazolo[3,4-*h*]-quinoline-7-carboxylic acid and its ethyl ester. Arkivoc 2009(12):322–336
233. Al-Dweik M, Zahra J, Khanfar M, El-Abadelah M, Zeller K, Voelter W (2009) Heterocycles [h]-fused to 4-oxoquinoline-3-carboxylic acid. Part VII: synthesis of some 6-oxoimidazo[4,5-h]quinoline-7-carboxylic acids and esters. Monatsh Chem 140:221–228
234. Sidorenko S (2006) Levofloxacin nowadays. Antibiot Chemother 51:28–37
235. Tunitskaya V, Khomutov A, Kochetkov S, Kotovskaya S, Charushin V (2011) Inhibiting DNA-gyrase by levofloxacin and other derivatives of fluoroheterocycles. Acta Nat 3:98–104

236. Dorgan R (1997) Preparation of pyrido[3,2,1-*i,j*]-1,3,4-benzoxadiazines as antibacterial agents. WO Patent 26261, 24 July 1997
237. Tanba H, Imai E, Mao S (2004) Preparation of optically active tricyclic compounds without forming diastereomers. JP Patent 99494, 2 Apr 2004
238. Wang B, Wang J (2002) Preparation of levofloxacin CN Patent 1357547, 10 Jan 2002
239. Wang J, Wang B (2002) The process comprises substituting 2,4,5-trifluoro-3-nitrobenzoyl fluoride with Cl_2 at 190–195 °C for 16-18 h to obtain 3-chloro-2,4,5-trifluorobenzoyl fluoride substituting. CN Patent 1357548, 10 Jan 2002
240. Shirato S (2007) Preparation of 3S-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid. JP Patent 210914, 23 Aug 2007
241. Patel M, Gupte S, Chugh Y, Saoji D, Agarwal S, deSouza N, Khorakiwala H (2000) Antibacterial optically pure benzoquinolizinecarboxylic acid derivatives processes, compositions and methods of treatment. WO Patent 68229, 16 Nov 2000
242. Yang Y, Ji R, Chen K (1999) A practical stereoselective synthesis of (S)-(-)-ofloxacin. Chin J Chem 17:539–544
243. Kim S, Kang S, Seo H, Kim J, Na H (2006) Cloning and characterization of ofloxacin ester-enantioselective lipase, and use for levofloxacin production. KR Patent 0109105, 19 Oct 2006
244. Lee S, Min B, Hwang S, Koo Y, Lee C, Song S, Oh S, Min S, Lin S, Kim D (2001) Enantioselective production of levofloxacin by immobilized porcine liver esterase. Biotechnol Lett 23:1033–1037
245. Lee S, Min B, Seong S, Oh S, Lim S, Kim S, Kim D (2001) Polyacrylamide gel immobilization of porcine liver esterase for the enantioselective production of levofloxacin. Biotec Bioprocess Eng 6:179–182
246. Kang S, Park S, Kim Y, Kim Y (1997) An improved synthesis of levofloxacin. Heterocycles 45:137–145
247. Lee B, Shin S (2002) Process for preparation of alkyl 2-(2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)) benzoyl-3(S)-((1-hydroxyprop-2-yl)amino)acrylate KR Patent 0026961, 13 Apr 2002
248. Lee B, Shin S (2001) 248. Ethyl 2-2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)benzoyl-3(S)-(1-hydroxyprophy-2-ylamino)acrylate and method for manufacturing the same. KR Patent 0018722, 15 Mar 2001
249. Lee B, Shin S (2001) Method for manufacturing ethyl 2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)benzoylacetate. KR Patent 0018721, 15 Mar 2001
250. Lee B, Shin S (2008) Process for preparation of levofloxacin WO Patent 077643, 7 Mar 2008
251. Kawakami K, Atarashi S, Kimura Y, Takemura M, Hayakawa I (1998) Synthesis and antibacterial activity of novel pyridobenzoxazine analogues. Chem Pharm Bull 46:1710–1715
252. Park Y, Lee H, Kim M, Kim K (2000) Preparation of (-)-pyrido-benzoxazine carboxylates from (+)-ethyl-2-(4-chloro-5-fluoro-2-halo-3-nitrobenzoyl)-3-[(1-hydroxypropy-2(S)-amino)]acrylate. WO Pat 50428, 31 Aug 2000
253. Kim Y, Kang S, Park S (1999) Method for the preparation of 9-fluoro-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid derivatives. US Patent 5952494, 14 Sep 1999
254. Adrio J, Carretero J, Ruano J, Pallares A, Vicioso M (1999) An efficient synthesis of ofloxacin and levofloxacin from 3,4-difluoroaniline. Heterocycles 51:1563–1572
255. Sato K, Takayanagi Y, Okano K, Nakayama K, Imura A, Iton M, Yagi T, Kobayashi Y, Nagai T (2001) Process for the preparation of benzoxazine derivatives and intermediates therefor. Eur Patent 1211254, 12 Feb 2001
256. Chupakhin O, Krasnov V, Levit G, Charushin V, Korolyova M, Tzoi E, Lee H, Park Y, Kim M, Kim K (2000) Preparation of (S)-benzoxazines and racemization of (R)-benzoxazines. JP Patent 178265, 17 June 2000
257. Charushin V, Krasnov V, Levit G, Korolyova M, Kodess M, Chupakhin O, Kim M, Lee H, Park Y, Kim K (1999) Kinetic resolution of (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazines with (*S*)-naproxen. Tetrahedron Asymmetry 10:2691–2695
258. Krasnov V, Levit G, Bukrina I, Andreeva I, Sh L, Sadretdinova L, Korolyova M, Kodess M, Charushin V, Chupakhin O (2003) Kinetic resolution of (±)-2,3-dihydro-3-methyl-4*H*-1,4-

benzoxazine, (±)-2-methyl-1,2,3,4-tetrahydroquino-line and (±)-2-methylindoline using *N*-tosyl-(*S*)-prolyl chloride. Tetrahedron Asymmetry 14:1985–1989
259. Krasnov V, Levit G, Kodess M, Charushin V, Chupakhin O (2004) *N*-phthaloyl-(*S*)-alanyl chloride as a chiral resolving agent for the kinetic resolution of heterocyclic amines. Tetrahedron Asymmetry 15:859–864
260. Krasnov V, Levit G, Andreeva I, Grishakov A, Charushin V, Chupakhin O (2002) Kinetic resolution of (±)-2-methyl-1,2,3,4-tetrahydroquinoline and (±)-2-methylindoline. Mendeleev Commun 12:27–29
261. Potemkin V, Krasnov V, Levit G, Bartashevich E, Andreeva I, Kuzminsky M, Anikin N, Charushin V, Chupakhin O (2004) Kinetic resolution of (±)-2,3-dihydro-3-methyl-4H-1,4-benzoxazine in the reaction with (S)-naproxen chloride: a theoretical study. Mendeleev Commun 14:69–71
262. Rueping M, Stoeckel M, Sugiono E, Theissmann T (2010) Asymmetric metal-free synthesis of fluoroquinolones by organocatalytic hydrogenation. Tetrahedron 66:6565–6568
263. Takemura M, Takahashi H, Kawakami K (1996) Preparation of pyridobenzoxazine derivatives as antibacterial agents. WO Patent 13370, 27 Sep 1996
264. Han C, Lee J, Lobkovsky E, Porco J (2005) Catalytic ester – amide exchange using group (IV) metal alkoxide – activator complexes. J Am Chem Soc 127:10039–10044
265. Cociorva O, Li B, Nomanbhoy T, Li Q, Nakamura A, Nakamura K, Nomura M, Okada K, Seto S, Yumoto K, Liyanage M, Zhang M, Aban A, Leen B, Szardenings A, Rosenblum J, Kozarich J, Kohno Y, Shreder K (2011) Synthesis and structure–activity relationship of 4-quinolone-3-carboxylic acid based inhibitors of glycogen synthase kinase-3β. Bioorg Med Chem Lett 21:5948–5951
266. Takamura M, Ohki H (2005) Preparation of pyridobenzoxazine derivatives as antibacterial agents. WO Patent 73238, 11 Aug 2005
267. Jefferson E, Swayze E, Osgood S, Miyaji A, Risen L, Blyn L (2003) Antibacterial activity of quinolone–macrocycle conjugates. Bioorg Med Chem Lett 13:1635–1638
268. Asahina Y, Takei M (2003) Preparation of 10-(3-cyclopropylaminomethyl-1-pyrrolidinyl) pyridobenzoxazinecarboxylic acid derivatives effective against resistant bacteria. WO Patent 78439, 25 Sep 2003
269. Bortolaso R, Stivanello M (2002) Process for the preparation of marbofloxacin via benzyl ether intermediates. IT Patent 1313683, 9 Sep 2002
270. Lipunova G, Nosova E, Charushin V, Sidorova L, Chasovskikch O (1998) 1,3,4-Oxa(thia) diazino [i, j]-annelated quinolines: a new type of key intermediate in the synthesis of tricyclic fluoroquinolones. Mendeleev Commun 8:131–133
271. Lipunova G, Sidorova L, Nosova E, Perova N, Charushin V, Aleksandrov G (1999) Derivatives of 1,3,4-thiadiazino[6,5,4-i, j]quinoline –new heterocyclic system. Zhurn Org Khim (Russ J Org Chem) 35:1729–1735
272. Lipunova G, Nosova E, Charushin V, Chasovskikh O (2001) Synthesis of fluorinated 1,3,4-oxadiazino[6,5,4-i, j]quinolines. Chem Heterocycl Compd 37:1278–1288
273. Nosova E, Sidorova L, Lipunova G, Mochul'skaya N, Chasovskikh O, Charushin V (2002) Synthesis of new fluorinated derivatives of quinolinecarboxylic acids. Chem Heterocycl Compd 38:922–928
274. Lipunova G, Nosova E, Mochul'skaya N, Andreiko A, Chasovskikh O, Charushin V (2002) 1,2,4-Triazino[5,6,1-i, j]quinolines: a new type of tricyclic analogs of fluoroquinolones. Russ Chem Bull 51:663–667
275. Nosova E, Lipunova G, Sidorova L, Charushin V (2001) New derivatives of 1,3,4-thiadiazino[6,5,4-i, j]quinoline. Russ J Org Chem 37:1169–1176
276. Nosova E, Lipunova G, Charushin V (2001) Synthesis and antibacterial activity of 1,3,4-thia(oxa)diazino[6,5,4-i, j]quinoline derivatives. Pharm Chem J 35:599–601
277. Lipunova G, Nosova E, Kravchenko M, Sidorova L, Tsoi E, Mokrushina G, Chasovskikh O, Charushin V (2004) Fluorinated quinolones possessing antituberculous activity. Pharm Chem J 38:597–601
278. Hu G, Zhang Z, Huang W (2004) Synthesis and antibacterial activity of new tetracyclic triazolothiadiazino fluoroquinolones. Chin Chem Lett 15:23–25

279. Miao H, Ceccetti V, Tabarrini O, Fravolini A (2000) New 1,8-*peri*-annelated tricyclic quinolone antibacterials. J Heterocycl Chem 37:297–302
280. Kwon Y, Na Y (2006) Study on the synthesis and cytotoxicity of new quinophenoxazine derivatives. Chem Pharm Bull 54:248–251
281. Schwaebe M, Nagasawa J, Haggach M (2008) Preparation of fused pyridone hydrazides as anticancer drugs. WO Patent 131134, 30 Oct 2008
282. Lipunova G, Mokrushina G, Nosova E, Rusinova L, Charushin V (1997) Novel pentacyclic fluoroquinolones. Mendeleev Commun 7:109–111
283. Nosova E, Lipunova G, Mokrushina G, Chasovskikh O, Rusinova L, Charushin V (1998) Novel pentacyclic fluoroquinolones. Zhurn Org Khim (Russ J Org Chem) 34:436–441
284. Charushin V, Nosova E, Lipunova G, Kodess M (2001) Fused fluoroquinolones: synthesis and ^{1}H and ^{19}F NMR studies. J Fluorine Chem 110:25–28
285. Wang E, Zhang X, Wu W (2003) Preparation of tetracyclic fluoroquinolonecarboxylates as antibacterial agents. CN Patent 1425668, 25 June 2003
286. Wang E, Zhang X, Wu B, Wu W (2003) Preparation of tetracyclic fluoroquinolonescarboxylates as antibacterial agents. CN Patent 1425669, 25 June 2003
287. Shaharyar M, Ali M, Abdullah M (2007) Synthesis and antiproliferative activity of 1-[(sub)]-6-fluoro-3-[(sub)]-1, 3,4-oxadiazol-2-yl-7-piperazino-1, 4-dihydro-4-quinolinone derivatives. Med Chem Res 16:292–299
288. Tabarrini O, Massari S, Daelemans D, Stevens M, Manfroni G, Sabatini S, Balzarini J, Cecchetti V, Pannecouque C, Fravolini A (2008) Structure–activity relationship study on anti-HIV 6-desfluoroquinolones. J Med Chem 51:5454–5458
289. Edmont D, Rocher R, Plisson C, Chenault J (2000) Synthesis and evaluation of quinoline carboxyguanidines as antidiabetic agents. Bioorg Med Chem Lett 10:1831–1834
290. Srivastava S, Chauhan P, Bhaduri A, Fatima N, Chatterjee R (2000) Quinolones: novel probes in antifilarial chemotherapy. J Med Chem 43:2275–2279
291. Dixit S, Mishra N, Sharma M, Singh S, Agarwal A, Awasthi S, Bhasin V (2012) Synthesis and in vitro antiplasmodial activities of fluoroquinolone analogs. Eur J Med Chem 51:52–59
292. Anderson V, Osheroff N (2001) Type II topoisomerases as targets for quinolone antibacterials turning Dr. Jekyll into Mr. Hyde. Curr Pharm Des 7:337–353
293. Zeng Q, Kwok Y, Kerwin S, Mangold G, Hurley L (1998) Design of new topoisomerase II inhibitors based upon a quinobenzoxazine self-assembly model. J Med Chem 41:4273–4278
294. Whitten J, Schwaebe M, Siddiqui-Jain A, Moran T (2005) Preparation of substituted quinobenzoxazine analogs as antitumor agents. US Patent 200585468, 21 Apr 2005
295. Whitten J, Pierre F, Schwaebe M (2006) Quinobenzoxazine analogs binding to G quartet structure in DNA and their preparation, pharmaceutical compositions, pharmacokinetics and use for treatment of proliferative diseases. WO Patent 113509, 26 Oct 2006
296. Kim M, Duan W, Gleason-Guzman M, Hurley L (2003) Design, synthesis, and biological evaluation of a series of fluoroquinoanthroxazines with contrasting dual mechanisms of action against topoisomerase II and G-quadruplexes. J Med Chem 46:571–583
297. Kwok Y, Zeng Q, Hurley L (1999) Structural insight into a quinolone-topoisomerase II-DNA complex. J Biol Chem 274:17226–17235
298. Schwaebe M, Ryckman D, Nagasawa J, Pierre F, Vialettes A, Haddach M (2011) Facile and efficient generation of quinolone amides from esters using aluminum chloride. Tetrahedron Lett 52:1096–1100
299. Kang D, Kim J, Jung M, Lee E, Jahng Y, Kwon Y, Na Y (2008) New insight for fluoroquinophenoxazine derivatives as possibly new potent topoisomerase I inhibitor. Bioorg Med Chem Lett 18:1520–1524
300. Duan W, Rangan A, Vankayalapati H, Kim M, Zeng Q, Sun D, Han H, Fedorov O, Nishioka D, Rha S, Lzbicka E, Von Hoff D, Hurley L (2001) Design and synthesis of fluoroquinophenoxazines that interact with human telomeric G-quadruplexes and their biological effects. Mol Cancer Ther 1:103–120
301. Kwok Y, Sun D, Clement J, Hurley L (1999) The quinobenzoxazines: relationship between DNA binding and biological activity. Anti-Cancer Drug Des 14:443–447

302. Azema J, Guidetti B, Dewelle J, Calve B, Mijatovic T, Korolyov A, Vaysse J, Malet-Martino M, Martino M, Kiss R (2009) 7-((4-Substituted)piperazin-1-yl) derivatives of ciprofloxacin: synthesis and *in vitro* biological evaluation as potential antitumor agents. Bioorg Med Chem 17:5396–5407
303. Whitten J, Schwaebe M, Siddiqui-J, Moran T (2004) Preparation of substituted quinolene analogs as antitumor agents. WO Patent 91504, 16 Feb 2004
304. Qin Y, Hurley L (2008) Structures, folding patterns, and functions of intramolecular DNA G-quadruplexes found in eukaryotic promoter regions. Biochimie 90:1149–1171
305. Kelland R (2005) Overcoming the immortality of tumour cells by telomere and telomerase based cancer therapeutics – current status and future prospects. Eur J Cancer 41:971–979
306. Parkinson G, Lee M, Neidle S (2002) Crystal structure of parallel quadruplexes from human telomeric DNA. Nature 417:876–880
307. Whitten J, Pierre F, Regan C, Schwaebe M, Yiannikouros G, Jung M (2006) Preparation of fused quinolone analogs which inhibit cell proliferation and/or induce cell apoptosis. US Patent 0063761, 6 Apr 2006
308. Hurley L, Guzman M (2007) Combination cancer chemotherapy. WO Patent 137000, 29 Nov 2007
309. Lipunova G, Nosova E, Mokrushina G, Sidorova L, Charushin V (2000) Antitumor activity of the fluorinated derivatives of condensed quinolines and quinazolines. Pharm Chem J 34:19–22
310. Lipunova G, Nosova E, Sidorova L, Charushin V (2011) Synthesis and antitumor activity of fluorinated derivatives of [i, j]-annelated quinolones. Pharm Chem J 45:208–210
311. Korolyov A, Dorbes S, Azema J, Guidetti B, Danel M, Lamoral-Theys D, Gras T, Dubois J, Kiss R, Martino R, Malet-Martino M (2010) Novel lipophilic 7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid derivatives as potential antitumor agents: improved synthesis and in vitro evaluation. Bioorg Med Chem 18:8537–8548
312. Wentland M, Aldous S, Gruett M, Perni R, Powles R, Danz D, Klingbeil K, Peverly A, Robinson R, Corbett T, Rake J, Coughlin S (1995) The antitumor activity of novel pyrazoloquinoline derivatives. Bioorg Med Chem Lett 5:405–410
313. Kamal A, Devaiah V, Reddy K, Kumar M (2005) Synthesis and biological activity of fluoroquinolone-pyrrolo[2,1-*c*][1,4]benzodiazepine conjugates. Bioorg Med Chem 13:2021–2029
314. Khire U, Liu X, Nagarathnam D, Wood J, Wang L, Liu D, Zhao J, Guernon L, Zhang L (2005) Quinolonecarboxylic acid derivatives for treatment of hyperproliferative conditions, their preparation and pharmaceutical compositions. WO Patent 097752, 20 Oct 2005
315. Qidong Y, Xungui H, Zhiyu L (2004) Preparation of quinolone derivatives as antitumor agents. CN Patent 1473827, 11 Feb 2004
316. Tomita K, Tsuzuki Y, Shibamori K, Tashima M, Kajikawa F, Sato Y, Kashimoto S, Chiba K, Hino K (2002) Synthesis and structure – activity relationships of novel 7-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acids as antitumor agents. Part 1. J Med Chem 45:5564–5575
317. Tsuzuki Y, Tomita K, Shibamori K, Sato Y, Kashimoto S, Chiba K (2004) Synthesis and structure – activity relationships of novel 7-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acids as antitumor agents. Part 2. J Med Chem 47:2097–2109
318. Tsuzuki Y, Tomita K, Sato Y, Kashimoto S, Chiba K (2004) Synthesis and structure–activity relationships of 3-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines as novel antitumor agents. Bioorg Med Chem Lett 14:3189–3193
319. Whitten J, Schwaebe M, Moran T (2004) Preparation of heterocyclic-substituted 1,4-dihydro-4-oxo-1,8-naphthyridine analogs. WO Patent 91627, 28 Jan 2004
320. Xu J, Cole D, Chang C, Ayyad R, Asselin M, Hao W, Gibbons J, Jelinsky S, Saraf K, Park K (2008) Inhibition of the signal transducer and activator of transcription-3 (STAT3) signaling pathway by 4-Oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylic acid esters. J Med Chem 51:4115–4121
321. Bryskier A, Lowther J (2005) Antituberculoses agents. In: Bryskier A (ed) Antimicrobial agents. ASM Press, Washington, DC

322. Aubry A, Pan X, Fisher M, Jarlier V, Cambau E (2004) *Mycobacterium tuberculosis* DNA gyrase: interaction with quinolones and correlation with antimycobacterial drug activity. Antimicrob Agents Chemother 48:1281–1288
323. Artico M, Nai A, Sbardella G, Massa S, Musiu C, Lostia S, Demontis F, Colla P (1999) Nitroquinolones with broad-spectrum antimycobacterial activity *in vitro*. Bioorg Med Chem Lett 9:1651–1656
324. Imramovsky A, Polanc S, Vinsova J, Kocevar M, Jampilek J, Reckova Z, Kaustova J (2007) A new modification of anti-tubercular active molecules. Bioorg Med Chem 15:2551–2559
325. Vavrikova E, Polanc S, Kocevar M, Horvati K, Bosze S, Stolarikova J, Vavrova K, Vinsova J (2011) New fluorine-containing hydrazones active against MDR-tuberculosis. Eur J Med Chem 46:4937–4945
326. Senthilkumar P, Dinakaran M, Banerjee D, Devakaram R, Yogeeswari P, China A, Nagaraja V, Sriram D (2008) Synthesis and antimycobacterial evaluation of newer 1-cyclopropyl-1,4-dihydro-6-fluoro-7-(substituted secondary amino)-8-methoxy-5-(substituted)-4-oxoquinoline-3-carboxylic acids. Bioorg Med Chem 16:2558–2569
327. Sharma K, Fernandes P (2006) Synthesis and biological activity of substituted quinolones derived from 6-fluoro-3-carbethoxy-1H-quinolin-4-one. Ind J Heterocycl Chem 15:253–258
328. Lakhina V, Zinchenko E, Yarotskij S, Charushin V, Chupakhin O, Tsoj E, Shorshnev S (1997) Antibiotic of rifamycin order showing antibacterial and antimycobacterial antituberculosis activity. RU Patent 2098419, 10 Dec 1997
329. Sheu J, Chen Y, Tzeng C, Hsu S, Fang K, Wang T (2003) Synthesis, and antimycobacterial and cytotoxic evaluation of certain fluoroquinolone derivatives. Helv Chim Acta 86:2481–2489
330. Fedorova O, Rusinov G, Mordovskoj G, Zueva M, Kravchenko M, Ovchinnikova I, Chupakhin O (1997) Synthesis and tuberculostatic activity of podands with fluoroquinoline fragment. Khim Farm Zhurn (Chem Pharm J) 31:21–23
331. Dinarakan M, Senthilkumar P, Yogeeswari P, China A, Nagaraja V, Sriram D (2008) Antimycobacterial activities of novel 2-(sub)-3-fluoro/nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-*a*]quinoline-6-carboxylic acid. Bioorg Med Chem 16:3408–3418
332. Dinarakan M, Senthilkumar P, Yogeeswari P, China A, Nagaraja V, Srieam D (2008) Novel ofloxacin derivatives: synthesis, antimycobacterial and toxicological evaluation. Bioorg Med Chem Lett 18:1229–1236
333. Bartel S, Kleefeld G, Schulze T, Paessens A, Neumann R, Reefschlaeger J, Streissle G (1994) Quinolone- and naphthyridinecarboxylic acids. DE Patent 4303657, 11 Aug 1994
334. Ceccetti V, Parolin C, Moro S, Pecere T, Filipponi E, Calistri A, Tabarrini O, Gatto B, Palumbo M, Fravolini A, Palu G (2000) 6-aminoquinolones as new potential anti-HIV agents. J Med Chem 43:3799–3802
335. Witvrouw M, Daelemans D, Pannecouque C (1998) Broad-spectrum antiviral activity and mechanism of antiviral action of the fluoroquinolone derivative K-12. Antivir Chem Chemother 9:403–411
336. Kimura T, Katsube T (1993) Preparation of aminoquinolone derivatives as anti-HIV agents. US Patent 5519016, 1 Dec 1993
337. Kimura T, Katsube T, Nishigaki T (1997) Preparation of trifluoromethyl(piperazinyl)quinolinecarboxylic acids as anti-HIV agents. JP Patent 09249568, 22 Sep 1997
338. Ohmine T, Katsube T, Tsuzaki Y, Kazui M, Kobayashi N, Komai T, Hagihara M, Nishigaki T, Iwamoto A, Kimura T, Kashiwase H, Yamashita M (2002) Anti-HIV-1 activities and pharmacokinetics of new arylpiperazinyl fluoroquinolones. Bioorg Med Chem Lett 12:739–742
339. Hagihara M, Kashiwase H, Katsube T, Kimura T, Komai T, Momota K, Ohmine T, Nishigaki T, Kimura S, Shimada K (1999) Synthesis and anti-HIV activity of arylpiperazinyl fluoroquinolones: a new class of anti-HIV agents. Bioorg Med Chem Lett 9:3063–3068
340. Tomoahi K, Toshinoro O, Hidekiho F, Masako T, Toshinoro N, Yoshinaki K, Tetsushi N (1998) Preparation and formulation of pyridobenzoxazinecarboxylic acid derivatives as virucides. WO Patent 33835, 7 Apr 1998

341. Pandeya S, Srirama D, Nathb G, DeClercqc E (2000) Synthesis, antibacterial, antifungal and anti-HIV activities of norfloxacin mannich bases. Eur J Med Chem 35:249–255
342. Ishimura M, Furukawa H, Katsube T (1999) Preparation of fluoroquinolones as anticytomegalovirus agents. WO Patent 42106, 26 Aug 1999
343. Selvam P, Rathore P, Karthikumar S, Velkumar K, Palanisamy P, Vijayalakhsmi S, Witvroum M (2009) Synthesis and antiviral studies of novel N-sulphonamidomethyl piperazinyl fluoroquinolones. Ind J Pharm Sci 71:432–436
344. Schneider S, Ruppelt M, Schriewer M, Schulze T, Neumann R (1993) 9-fluoro-7-oxo-7H-pyrido(1,2,3-de)(1,4)benzoxazine carboxylic acids and esters, and their use as antiviral agents. Patent EP 563734, 6 Oct 1993
345. Schneider S, Bartel S, Ruppelt M, Sriewer M, Schulze T, Neumann R (1993) 7-oxo-7H-pyrido(1,2,3-de)(1,4)benz-oxazinecarboxylic acids and esters and their use as antiviral agents. Patent EP 563732, 6 Oct 1993
346. Gabardi S, Waikar S, Martin S, Roberts K, Chen J, Borgi L, Sheashaa H, Dyer C, Malek S, Tullius S, Vadivel N, Grafals M, Abdi R, Najafian N, Milford E, Chandraker A (2010) Evaluation of fluoroquinolones for the prevention of BK viremia after renal transplantation. Clin J Am Soc Nephrol 5:1298–1304
347. Anquetin G, Greiner J, Vierling P (2005) Synthesis of mono- and di-substituted 2,4,5-trifluorobenzoic acid synthons, key precursors for biologically active 6-fluoroquinolones. Tetrahedron 61:8394–8404
348. Abdul-Rahman S (1999) Preparation of quinolonecarboxylates as bactericides and paraziticides. US Patent 6,967,205, 15 Nov 1999
349. Watanuki S, Kogo Y, Moritomo H, Tsukamoto I, Kaga D, Okuda T, Hirayama F, Moritani Y, Takasaki J (2005) Preparation of quinolone derivatives as platelet aggregation inhibitors WO Patent 009971, 3 Feb 2005
350. Yang F, Shipe W, Bunda J, Nolt M, Wisnoski D, Zhao Z, Barrow J, Ray W, Ma L, Wittmann M, Seager M, Koeplinger K, Hartman G, Lindsley C (2010) Parallel synthesis of *N*-biaryl quinolone carboxylic acids as selective M_1 positive allosteric modulators. Bioorg Med Chem Lett 20:531–536
351. Kuduk S, DiMarco C, Cofre V, Pitts D, Ray W, Ma L, Wittmann M, Seager M, Koeplinger K, Thompson C, Hartman G, Bilodeau M (2010) Pyridine containing M_1 positive allosteric modulators with reduced plasma protein binding. Bioorg Med Chem Lett 20:657–661
352. Kuduk S, DiMarco C, Cofre V, Pitts D, Ray W, Ma L, Wittmann M, Veng L, Seager M, Koeplinger K, Thompson C, Hartman G, Bilodeau M (2010) N-heterocyclic derived M_1 positive allosteric modulators. Bioorg Med Chem Lett 20:1334–1337
353. Kuduk S, DiMarco C, Cofre V, Ray W, Ma L, Wittmann M, Seager M, Koep[linger K, Thompson C, Hartman G, Bilodeau M (2011) Fused heterocyclic M1 positive allosteric modulators. Bioorg Med Chem Lett 21:2769–2772
354. Toffoli P, Rodier N (1987) Méthanesulfonate de péfloxacinium (péflacine DCI). Acta Crystallogr Sect C 43:1745–1748
355. Turel I, Leban I, Zupancic M, Bukovec P, Gruber K (1996) An adduct of magnesium sulfate with a member of the quinolone family (Ciprofloxacin). Acta Crystallogr Sect C 52:2443–2445
356. Hashimoto K, Fujita N, Tanaka T, Kido M (1995) 6-ethyl-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidino)-5-methyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinoli-zine-2-carboxylic acid. Acta Crystallogr Sect C 51:519–521
357. Anacona J, Toledo C (2002) Synthesis and antibacterial activity of metal complexes of ciprofloxacin. Trans Met Chem 26:228–236
358. Jakics E, Iyobe S, Hirai K, Fukuda H, Hashimoto H (1992) Occurrence of the nfxB type mutation in clinical isolates of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 36:2562–2567
359. Turel I (2002) The interactions of metal ions with quinolone antibacterial agents. Coord Chem Rev 232:27–47
360. Lipunova G, Nosova E, Charushin V (2009) Metal complexes of fluoroquinolonecarboxylic acids. Russ Chem J 53:74–85

361. Serafin A, Stanczak A (2009) The complexes of metal ions with fluoroquinolones. Russ J Coord Chem 35:83–97
362. Saha D, Padhye S, Anson C, Powell A (2002) Hydrothermal synthesis, crystal structure, spectroscopy, electrochemistry and antimycobacterial evaluation of the copper (II) ciprofloxacin complex: $[Cu(cf)_2(BF_4)_2]\cdot 6H_2O$. Inorg Chem Commun 5:1022–1027
363. Efthimiadou E, Sanakis Y, Katsarou M (2006) Antibacterial activity of enrofloxacine metallocomplexes. J Inorg Biochem 100:1378–1388
364. Katsarou M, Efthimiadou E, Psomas G, Karaliota A, Vourloumis D (2008) Novel copper(II) complex of N-propyl-norfloxacin and 1,10-phenanthroline with enhanced antileukemic and DNA nuclease activities. J Med Chem 51:470–478
365. Shingnapurkat D, Bucther R, Afrabiasi Z, Sinn E, Ahmed F, Sarkar F, Padhye S (2007) Neutral dimeric copper–sparfloxacin conjugate having butterfly motif with antiproliferative effects against hormone independent BT20 breast cancer cell line. Inorg Chem Commun 10:459–462
366. Patitungkho S, Absule S, Dandawate P, Padhye S, Ahmad A, Sarkar F (2011) Synthesis, characterization and anti-tumor activity of moxifloxacin–copper complexes against breast cancer cell lines. Bioorg Med Chem Lett 21:1802–1806
367. Gao F, Yang P, Xie J, Wang H (1995) Norfloxacin metallocomplexes: structure and antibacterial activity. J Inorg Chem 60:61–67
368. Jimenez-Garrido N, Perello L, Ortiz R (2005) Cobalt and copper complexes of ciprofloxacine. J Inorg Biochem 99:677–689
369. Xiao D, Wang E, An H, Su Z, Li Y, Gao L, Sun C, Xu L (2005) Rationally designed, polymeric, extended metal–ciprofloxacin complexes. Chem Eur J 11:6673–6686
370. Chen Z, Xiong R, Zhang J, Chen X, Xue Z, You X (2001) 2D molecular square grid with strong blue fluorescent emission: a complex of norfloxacin with zinc(II). Inorg Chem 40:4075–4077
371. Tarushi A, Psomas G, Raptopoulou C, Psycharis V, Kessissoglou D (2009) Structure and DNA-binding properties of bis(quinolonato)bis(pyridine)zinc(II) complexes. Polyhedron 28:3272–3278
372. Drevensek P, Kosmrlj J, Giester G (2006) Spectral study of ofloxacine coordination. J Inorg Biochem 100:1755–1763
373. Sakai M, Hara A, Anjo S, Nakamura M (1999) Al (III) complexes of fluoroquinoline formation: NMR study. J Pharm Biomed Anal 18:1057–1067
374. Polishchuk A, Gerasimenko A, Gayvoronskaya K, Karaseva E (2008) Tetrakis(dihydrogen pefloxacinium) di-μ2-chlorido-bis-[tetrachloridobismuthate(III)] tetrachloride octahydrate. Acta Crystal E 64:m931–m932
375. Vieira L, deAlmeida M, Lourenco M, Bezerra A, Fontes A (2009) Synthesis and antitubercular activity of palladium and platinum complexes with fluoroquinolones. Eur J Med Chem 44:4107–4111
376. Vieira L, deAlmeida M, de Abreu H, Duarte H, Grazul R, Fontes A (2009) Platinum(II) complexes with fluoroquinolones: synthesis and characterization of unusual metal–piperazine chelates. Inorg Chim Acta 362:2060–2064
377. Sun C, Ping H, Zhang M, Li H, Guan F (2011) Spectroscopic studies on the lanthanide sensitized luminescence and chemiluminescence properties of fluoroquinolone with different structure. Spectrochim Acta A Mol Biomol Spectrosc 82:375–382